National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 21 Highlights
June 11-13, 2001
U.S. Department of Transportation
DOT Headquarter/Nassif Building, Rooms 8236-8240
400 7th Street, S. W., Washington, D. C.

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with welcoming remarks along with AEGL Program Director, Roger Garrett, who also welcomed the committee members and guests. Thanks were conveyed to George Cushmac for making the necessary arrangements for the meeting and to the Department of Transporation (DOT) for providing the facilities.

The approval of the meeting highlights for NAC/AEGL-20 were postponed until John Morawetz's arrival in the afternoon since he had provided input for the revision of the hydrogen cyanide section as well as other sections. After a brief period of review and discussion, a motion was made by Mark McClanahan and seconded by Doan Hansen to approve the meeting highlights with minor editorial changes. The revised highlights of NAC/AEGL-20 are attached (Appendix A). The motion was unanimously approved (Appendix B).

The highlights of the NAC/AEGL-21 meeting are presented below along with the meeting agenda (Attachment 1) and the attendee list (Attachment 2). Ballots were taken during the meeting and are incorporated into the appropriate chemical-specific section.

GENERAL INTEREST ITEMS

Roger Garrett expressed the importance of the AEGL development process and the valuable contributions of the NAC/AEGL Committee. The AEGL values developed by the committee are extremely useful for many domestic and international groups. More input from these groups on the overall development of the AEGL values is expected in the future.

The next meeting was set for September 11-13, 2001, at this same DOT facility. At the suggestion of John Hinz, the last meeting of the year will be held (tentatively) from December 3-7, 2001, in San Antonio, Texas. After local lodging arrangements are finalized, John Hinz will notify the NAC/AEGL members and guests.

REVIEW OF PRIORITY CHEMICAL FOR AEGL VALUES

BORON TRIFLUORIDE, CAS Reg. No. 763-07-2

Boron Trifluoride: Dimethyl ether, CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Honeywell, NAC/AEGL Chair
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

The review was presented by Claudia Troxel (Attachment 3). Quantitative toxicity data were not available for the boron trifluoride:dimethyl ether complex. Because the complex breaks down into dimethyl ether and boron trifluoride, the AEGL derivations were based upon boron trifluoride toxicity data alone. The following summary is what was proposed, but no vote was taken. These values are to be reconsidered at the next AEGL meeting.

The proposed AEGL-1 derivation is based upon the statement that a concentration of 1.5 ppm (4.1 mg/m^3) boron trifluoride has a "rather pleasant acidic odor," indicating that the odor threshold had been reached. Although the worker noted the smell of boron trifluoride to be pleasant, it is likely that others would find the odor unpleasant. This level does appear to be near the threshold for irritant effects: the subchronic study by Rusch et al. (1986) reports that minimal signs of irritation were noted in rats exposed to 2 or 6 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks. An interspecies uncertainty factor was not needed, and an intraspecies uncertainty was not applied to account for inter-individual differences because the odor was not irritating. The value was set equal for all AEGL time-points because the endpoint is based on odor.

Data were not available for derivation of an AEGL-2. Because data meeting the definition of an AEGL-2 defined endpoint were not available and the dose-response curve for lethality was steep (Rusch et al, 1986), it was proposed that the AEGL-3 levels be divided by 3 to obtain an estimate of the AEGL-2.

The proposed AEGL-3 derivation is based upon the 4-hour LC_{50} value of 1200 mg/m^3 determined by Rusch et al. (1986). An interspecies uncertainty factor of 10 was applied because there appeared to be some species differences in sensitivity to boron trifluoride, with the guinea pig being the most sensitive to lethality. An intraspecies uncertainty factor of 3 was applied based on the evidence that boron trifluoride acts as an irritant.

Experimentally derived exposure values are scaled to AEGL time frames using the default value of $n = 1$ for extrapolating from shorter to longer exposure periods and a value of $n = 3$ to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it is not considered appropriate to extrapolate from a 4-hour to a 10-minute time point.

The proposed values are listed in the tables below. AEGL values are given in terms of mg/m^3 because boron trifluoride gas becomes an aerosol upon contact with moisture in the air.

Summary of AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3
AEGL-2	27 mg/m^3	27 mg/m^3	21 mg/m^3	13 mg/m^3	6.7 mg/m^3
AEGL-3	80 mg/m^3	80 mg/m^3	63 mg/m^3	40 mg/m^3	20 mg/m^3

Several NAC/AEGL members thought that the guinea pig appeared to be more sensitive. A question arose as to whether there was a sex differential in the studies. It was reported that it was minimal. Further questions concerned the time at which the signs of toxicity appeared in the study and the possibility of using a BMD approach with the data. It was also mentioned that obtaining the individual animal data from the Rusch et al. study might prove useful. Final conclusion was that these comments and suggestions will be addressed in a revised TSD for final review in the next meeting.

CHLORINE DIOXIDE, CAS Reg. No. 10049-04-4

Chemical Manager: Robert Benson, US EPA
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented a review of the Chlorine Dioxide TSD (Attachment 4) and described a summary of an unpublished industrial study from the 1950s (DuPont) that had not yet been obtained by the committee. After extensive discussion it was decided that data were insufficient for development of AEGL-1 values. Ernie Falke made a motion, seconded by Robert Benson, not to develop AEGL-1 values for chlorine dioxide. The motion carried for AEGL-1 [YES: 24, NO: 0, Abstain:2] (Appendix C).

AEGL-3 values were based on a study showing no lethality in rats exposed to 26 ppm for 6 hours (Dupont, 195x). As rats appear not to be the most sensitive species, an interspecies uncertainty factor of 10 was applied. Chlorine dioxide is highly reactive and causes a variety of serious adverse effects in the lung that are likely a direct chemical effect on the tissue in the lung. As this effect is not likely to vary greatly among individuals, an intraspecies uncertainty factor of 3 was used. Thus, a total uncertainty factor of 30 was applied. The default values of the exponent 'n' (n =1 for 8-hours, and n=3 for 10-min, 30-min, 1-hr and 4-hr) were applied for scaling across time. The motion was made by Bob Snyder and seconded by John Hinz to adopt the AEGL-3 values presented in the table below. The motion was approved [Yes: 24; No:2; Abstain: 0] (Appendix C).

AEGL-2 values were obtained by dividing the AEGL-3 values by 3 as there is no appropriate study using a single exposure showing effects consistent with the definition of AEGL-2. This

approach is supported by several repeat-exposure studies in rats. A motion was made by Mark McClanahan and seconded by Larry Gephart to accept the AEGL-2 values presented in the table below. The motion was approved [YES: 17; No: 6 Abstain: 3] (Appendix D).

The values for chlorine dioxide are contingent on obtaining the DuPont study and verifying that the summary used accurately reflects the study design and results. If this is the case, then the revised TSD will be provided to the NAC/AEGL for approval. Otherwise, the NAC/AEGL will discuss this chemical at a future meeting.

Proposed AEGL Values for Chlorine Dioxide

	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.97 ppm	0.67 ppm	0.53 ppm	0.32 ppm	0.21 ppm
AEGL-3	2.9 ppm	2.0 ppm	1.6 ppm	0.97 ppm	0.63 ppm

NR=Not Recommended

N, N-DIMETHYL FORMAMIDE, CAS Reg. No.68-12-2

Chemical Manager: Loren Koller, OSU
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

Claudia Troxel presented an overview of available data/information on production, physical aspects and exposure effects of N, N-dimethyl formamide (DMF) (Attachment 5).

The AEGL-3 was based on a study by MacDonald (1982) in which groups of 3 male and 3 female rats were exposed to 3700 ppm DMF for 1 or 3 hours with no mortality, while exposure for 7 hours resulted in 83% mortality. Clinical signs were limited to excess grooming in all exposure groups, with lethargy additionally noted in rats exposed for 7 hours. A no-effect level for lethality at 3700 ppm for 3 hours was chosen for the derivation. A total uncertainty factor of 30 was applied to the data. An interspecies uncertainty factor of 3 was applied based upon the fact that the mechanism of toxicity is believed to be related to the metabolism of DMF, and evidence indicates that the primary enzyme responsible for metabolism of DMF (P450 2E1) is similar in both rats and humans. Additionally, occupational exposures in humans demonstrate similar hepatic effects as those seen in animals (cats, mice, rats) following repeated exposure to DMF. Although the mechanism of action has not yet been clearly defined, limited species differences have been identified in the manifestation of toxicity. An intraspecies uncertainty factor of 10 was applied to account for inter-individual differences in levels of P450 2E1 (which can be induced by alcohol consumption). Additionally, based upon the proposed mechanism of action, detoxification of the reactive intermediate is dependent upon conjugation with glutathione. If glutathione levels are depleted due to other reasons, the potential exists for greater exposure to the reactive intermediate. AEGL-3 values were scaled across time using an

n=3 for extrapolation to 10 and 30 minutes and 1 hour, and an n=2 for extrapolation to 4 or 8 hours. A default value of n of 2 was chosen instead of a default value of n of 1 based on available human data in which individuals were exposed up to 87 ppm DMF for 4 hours with no reported effects. A default value of n of 1 would result in AEGL values that are inconsistent with these data. A motion to adopt the values of AEGL-3 (in table below) was made by Loren Koller and seconded by Richard Thomas. The motion was approved [YES:15; NO: 6; Abstain: 5] (Appendix D).

AEGL-2: Data meeting the definition of an AEGL-2 defined endpoint were not available. Therefore, a motion to use the AEGL-3 value and divide by 2 was proposed by Jonathan Borak and seconded by Loren Koller. The motion was approved [YES:14; NO: 7; Abstain: 5] (appendix D).

AEGL-1: Ernie Falke immediately proposed a motion that the Committee not recommend a value for AEGL-1; it was seconded by George Rogers. The motion was approved [YES:20, NO: 5; Abstain: 0] (Appendix D).

Later, it was suggested that the Committee request data from major producers to improved the quality of TSD, if new data become available. After the vote, there was a considerable discussion on AEGL-1 , the Committee again decided there were insufficient data to set an appropriate value though some thought that enzyme changes fall under the AEGL-1 definition. It was noted that the IARC suggestions should be addressed before we leave the chemical.

Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	160 ppm	110 ppm	90 ppm	55 ppm	38 ppm
AEGL-3	320 ppm	220 ppm	180 ppm	110 ppm	76 ppm

REVIEW OF CHEMICALS WITH ISSUES FROM PREVIOUS MEETINGS

HYDROGEN CYANIDE : revisit of AEGL-1

Chemical Manager: George Rodgers, AAPCC
Staff Scientist: Sylvia Talmage, ORNL Staff Scientist

The discussion focused on the supporting scientific evidence of AEGL-1 values as pointed out by John Morawetz. George Rodgers and Sylvia Talmage proposed three options to handle the matter (Attachment 6). The committee agreed that option 3 be used with the added statement, "The committee agreed the Leeser study generally supported the approved NAC/AEGL values. It is used as supporting evidence for AEGL-1 values derived from El Ghawabi et al., (1975)." The AEGL-1 values are 2.5 , 2.5, 2.0, 1.3, and 1.0 ppm for the 10-min, 30 min, 1 hr, 4 hr, and 8 hr time periods, respectively as approved at the NAC/AEGL-19. Following this change, the committee approved the Meeting-20 Highlights (Appendix B, Refer to the INTRODUCTION Section).

PHOSGENE:

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented Comments received from the *Federal Register Notice* of January, 2001 (Attachment 7) There were questions on why the NAC/AEGL adopted the 30-minute AEGL-2 as the 10-minute AEGL-2 rather then extrapolating. This approach was used since extrapolating would yield a value similar to concentrations causing alveolar pulmonary edema in rats. A motion to retain the current values (10-minute AEGL-2 of 0.60 ppm and 30-minute AEGL-2 of 0.60 ppm) was made by George Rogers and seconded by Ernie Falke. The motion carried unanimously (Appendix E). Another motion was then made by John Hinz and seconded by Mark McClanahan to elevate AEGL values from proposed to interim status. The vote was unanimous by a show of hands (Appendix E).

XYLENES:

Chemical Manager: Loren Koller, OSU
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

The reevaluation of the AEGLs using the additional information provided by PBK modeling was presented by Claudia Troxel (Attachment H). Additionally, Ursula Gundert-Remy provided the modeling information (Attachment I). At the January 2000 NAC/AEGL meeting, AEGL-2 and -3 values were set equal across time based on the endpoint of central nervous system effects. It was felt by some of the committee that the 10- and 30-minute AEGL-2 and -3 values were too

low. Therefore, PBK modeling was performed to determine 10- and 30-minute AEGL-2 and -3 values. Ursula Gundert-Remy performed the modeling for — and p-xylene assuming a 1-compartment model. Kinetics for — and p-xylene were calculated from data on pp 52 of the draft 12/2000 TSD

m-xylene	10 min	30 min
AEGL-2	1200 ppm	570 ppm
AEGL-3	2500 ppm	1200 ppm

p-xylene	10 min	30 min
AEGL-2	3100 ppm	1200 ppm
AEGL-3	6700 ppm	2600 ppm

By show of a straw ballot (hands) the votes were essentially split over 1) Entirely using the modeling numbers derived for m-xylene, 2) Using modeling numbers for both time intervals (1 to 8 hr model data), or 3) Using the older straight line numbers. No final votes were balloted, but the NAC/AEGL would like to look at the 95% C.L. for the next meeting and see if it could be incorporated into the TSD document. Ursula Gundert-Remy will be prepared to lead the discussion.

HYDROGEN SULFIDE:

Chemical Manager: Steve Barbee, Arch Chemicals, Inc.
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Steve Barbee led the discussion and explained that members of the NAC/AEGL had provided questions on potential studies for AEGL-1 development. Zarena Post presented the Texas Natural Resource Conservation Commission's (TNRCC's) response to questions posed by the NAC/AEGL committee members on the report by the Laboratory and Mobile Monitoring Section of the TNRCC, "Corpus Christi Mobile Laboratory Trip, January 31-February 6, 1998; Real-Time Gas Chromatography and Composite Sampling, Sulfur dioxide, Hydrogen sulfide, and Impinger Sampling" and answered questions from the floor. Figures were presented on overheads that showed the concentrations of H_2S measured by 2 separate sampling vans over the course of the sampling trip and the times that staff reported symptoms (Attachment 10). Questions concerned whether health effects could be attributed to hydrogen sulfide exposure, the accuracy of the analytical measurement techniques, possible concurrent exposures, and comparisons results from the two monitoring vans.

Cheryl Bast then presented answers to questions on the Jappinen et al., 1990, and Bhambhani et al., 1994 & 1996, studies (Attachment 11). These questions revolved around comparing the actual concentrations of hydrogen sulfide inhaled in the TNRCC vs. Bhambhani and Jappinen studies, concentration-response relationships, and differences in health effects between oral and nasal exposures. Steve Barbee then compared the Jappinen, Bhambhani and Texas studies with regard to methodology and observed effects/applicability to AEGL-1 development. A motion was made by John Hinz and seconded by George Rogers that the committee adopt an AEGL-1

based on headaches in asthmatic humans exposed to 2 ppm for 30 minutes (based on the Jappinen et al 1990 report). An uncertainty factor of 3 was applied since asthmatics may not be more sensitive than healthy individuals to headache induction. A modifying factor of 3 was also applied to account for the fact that headache may be more severe than endpoints defined by AEGL-1 and because of the shallow concentration-response curve for hydrogen sulfide. Values were scaled across time using the chemical-specific exponent of n = 4.36. The motion carried. (YES: 20; NO: 4; Abstain: 3) (Appendix F).

Proposed AEGL-1 Values for Hydrogen Sulfide

	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.25 ppm	0.20 ppm	0.17 ppm	0.12 ppm	0.11 ppm

TOPICAL ITEMS FOR DISCUSSION

USE OF ODOR IN AEGL-1 DEVELOPMENT:

The consideration of odor in AEGL-1 development to be presented by Marc van Raaij was deferred to the September meeting.

USE OF RD_{50} DATA FOR DEVELOPMENT OF AEGLs

Larry Gephart presented an outline (Attachment 12) showing the location of irritation sites in the respiratory tree. Sensory irritation stimulates the trigeminal nerve and nerves in the respiratory mucosa, while olfaction is sensed by Cranial Nerve 1 and specialized areas in the nasal area. The Yves Alarie method of determining sensory irritation was examined in the presentation. Both immediate and delayed responses were noted in the data. Mechanistic considerations were deemed important. Comments from other Committee members included: Whether hypoxia stimulated respiration and the difference in feed-back mechanisms between the two sites of stimulation. Other areas of consideration concerned differences in species response due to postural changes to avoid irritant exposure and individual and anatomical differences. The effects of time vs. breathing rates for 30-minute exposures to primary irritants and other chemicals were shown on the handouts. A question of recovery and possible adaption was noted with the information that some researchers have produced a conditioned response to exposure. It was suggested that RD_{50} values should not be based on chemicals that produce a mixed irritation response (sensory + pulmonary). It was suggested that the NAC look at available human data and compare the level of response to animal data. Committee members noted that there are several literature reviews that address irritancy data. At the close of the discussion, Larry Gephart requested that any data or literature citations that might be helpful in addressing the subject be sent to him.

John Hinz outlined the use and application of the American Society for Testing and Materials (ASTM) Standard Method E981-84 (re-approved 1996)(Attachment 13). E981-84 is based on Dr.

Yves Alarie's research published between 1966-82 and serves as the experimental design for the studies now under contract at ExxonMobil Biomedical Sciences, Inc., in New Jersey. These studies will attempt to quantitatively and comparatively characterize the potential of various jet fuels to cause respiratory tract sensory irritation.

The need for these studies was triggered a) by the United States Air Force (USAF) and the Department of Defense program to replace JP-4 with a heavier, less volatile fuel, JP-8; and, b) by the NAC/AEGL) targeting JP-8 for review. The NAC/AEGL specifically recommended that the USAF include irritancy studies – specifically Alarie's upper respiratory tract sensory irritation assay – in its study plans for JP-8. The NAC/AEGL expects to incorporate such data into its risk assessment for JP-8. To address this request, the USAF in concert with Army and Navy colleagues designed a comparative study using JP-4, JP-8 and JP-8+100 using a protocol predicated on "E 981-84" to characterize and compare the relative potency of three jet fuels to cause respiratory tract sensory irritation.

Per protocol, these fuels are being administered for 30 minute periods by means of a head-only exposure system to groups of four male Swiss-Webster mice. Test atmospheres laden with these fuels are presented as vapor-only (JP-4) or as a vapor/aerosol mixtures (JP-8, JP-8+100), depending on the physicochemical properties of the fuels. Analytical sampling data should reveal differences in the distribution and relative proportions of the hydrocarbon species contained in the vapor and aerosol phases, and permit construction of each fuel's dose/response curve. Each fuel's RD50 will be derived from these curves and their propensity for respiratory tract sensory irritation compared. John Hinz expects to report his findings to the NAC/AEGL at its December'01 meeting in San Antonio.

SENSITIVITY OF CHILD ASTHMATICS VS ADULT ASTHMATICS IN ACUTE EXPOSURES

An issue of the sensitivity of child asthmatics vs adult asthmatics with regard to acute exposures was addressed by Ernie Falke. Ernie presented the review of asthmatics and their relative susceptibility to acute exposure in a lengthy attachment (Attachment 14). The issues as set forth in his review were: 1) Are normal children more susceptible than normal adults to irritant gases, and 2) Are asthmatic children or adolescents more susceptible than adult asthmatics to exposure to irritant gases? His report indicated a definitive answer to these questions requires specific data sets to allow appropriate comparisons: nonasthmatic children and healthy adults and asthmatic children and asthmatic adults. In both cases, exposures would be to a range of concentrations of irritants sufficient to determine a threshold for a specific type and level of physiologically significant response. Relative susceptibilities of healthy and asthmatic individuals were considered and presented by AEGL levels. There are no data to support the concern that child asthmatics are more sensitive to exposure to irritant gases than adult asthmatics.

PRESENTATION OF KAIF: A COMPUTER-BASED SYSTEM TO EVALUATE POISONINGS

Boris Filatov, Director, and Vladimir Tchernov, Assistant Director, of the South Center for

Chemical Emergencies of Volgograd, Russia, presented an overview of a computer-based system designed to recognize poisoning based on symptomatology following exposure to a toxic chemical. Boris and Vladimir noted that the South Center for Chemical Emergencies, Institute of Hygiene, Toxicology and Occupational Pathology in Volgograd, Russia, was founded in 1971 as a direct result of the Cold War and chemical weapons production. Several thousand clinical histories with symptomatologies were compiled in the files. The Poisoning Differential Diagnostics Computer Software System (KAIF) (Attachment 15) is designed to both help in consultations with medical doctors and also train medical students. It contains two different inter-related software programs: DEFIT which is designed to recognize a chemical substance causing an acute neurotoxic action, and NEUROTOPIC which determines the most afflicted area in the nervous system. The committee thanked Boris and Vladimir for their interesting and informative presentation.

COMMENTS AND RESPONSE ON *FEDERAL REGISTER* CHEMICALS: 66 FR21940, May 2, 2000

DIBORANE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by Jim Holler and seconded by Doan Hansen. The motion was approved unanimously by the NAC/AEGL (Appendix G).

BORON TRICHLORIDE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by Mark McClanahan and seconded by John Hinz. The motion was approved unanimously by the NAC/AEGL (Appendix H).

CARBON MONOXIDE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by John Hinz and seconded by Mark McClanahan. The motion was approved unanimously by the NAC/AEGL (Appendix I).

CHLOROMETHYL METHYL ETHER

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion was made by John Hinz and seconded by Mark McClanahan to move the chemical from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix J).

PERCHLOROMETHYL MERCAPTAN

One *Federal Register Notice* response was received from Tomen Agro (Attachment 16). The comments were: the subchronic studies were not appropriate for short term exposure, an UF of 3

x UF of 3 was only 9, the proposed 8-hour AEGLs for PMM are overly conservative when compared to 8-hour acceptable exposure levels set by other organizations, the need to establish an AEGL for PMM is not clear, and that Section B of the Notice is misleading as to the ability of certain individuals to detect chemicals relative to the AEGLS.

Reply: Chemical Manager, Zarena Post, addressed the comments. Zarena noted that we could reassess the studies. Zarena also noted that the UF is really the square root of 10, or 3.2. The NAC/AEGL noted that comparing AEGL values with the OSHA values is like comparing apples and oranges. The OSHA values are for chronic exposure of workers and limits, while the AEGL values are for the general public and acute single exposures. Chairman George Rusch suggested that Zarena send a letter of response within 60 days, and request that if there is additional data to consider, it be made available for consideration in a revision of the TSD and be discussed at the September meeting. A motion to elevate the chemical to interim status was made by John Hinz and seconded by Mark McClanahan. The motion was approved unanimously by the NAC/AEGL (Appendix K).

TETRANITROMETHANE

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 6). The state agreed with the derived AEGL values for tetranitromethane. However, MDEQ questioned that the cancer assessment in the TSD would have yielded a higher potency value (and lower allowed exposures) if the incidence for adenoma/adenocarcinomas in the lung of the male mouse instead of the female mouse had used for the calculation.

Reply: Chemical Manager, Bill Bress addressed the concern. The NAC/AEGL replied that a review of the Global 86 runs conducted showed that the slope factor was ~5 % higher by using the female than the male data. The reason for the discrepancy between the MDEQ and the NAC/AEGL results is unclear. The MDEQ did not describe their method of calculating the slope factor using the males. MDEQ's questioning of the appropriateness of estimating lifetime cancer risk from acute exposure is perhaps the most important point here and the NAC/AEGL concluded that the 5 % difference in potency factors is of no practical significance. NAC/AEGL will adopt the AEGL values as published in the *Federal Register Notices* of May 2, 2001. A motion to elevate the chemical from proposed to interim status was made by Mark McClanahan and seconded by Bill Bress. The motion was approved unanimously by the NAC/AEGL) (Appendix L).

TOLUENE

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 7). The MDEQ commented that overall the AEGLs for Toluene seemed to be well reasoned. However, the 10-min. AEGL-1 of 260 ppm and the 30-min. AEGL-2 of 270 ppm may be disproportionately close, but this could simply be reflective of a high threshold for irritation.

Reply: The comment was addressed by Chemical Manager Larry Gephart. The NAC/AEGL agreed that toluene concentrations of 260 ppm and 270 ppm are virtually identical. However, given the 3-fold difference in duration, the potential uptake of toluene could be 3-fold higher at 270 ppm for 30 minutes than 260 ppm for 10 minutes. Also, the concentration of toluene producing AEGL-1 effects (headache, eye irritation) are relatively close to those producing AEGL-2 effects (uncoordination, mental confusion). Hence, the "overlapping" noted occurs throughout the proposed scheme (e.g. , the 30 min. AEGL-1 value of 120 ppm is relatively close to the 1 hour. AEGL-2 value of 190 ppm). All AEGL-1 and -2 values were derived using n=2. So, the NAC/AEGL concluded that the proposed scheme is scientifically valid and should be maintained. A motion was made by Larry Gephart and seconded by Richard Thomas to elevate toluene from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix M).

FURAN

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 8). MDEQ expressed concerns in the following areas: l) A NOAEL was not identified in the only quantitative toxicology study by Terrill et al. (1989), and 2) applying uncertainty factors in the development of AEGL-2 and -3, especially the LOAEL to NOAEL conversion for the AEGL-2.

Reply: Chemical manager George Rogers responded to the comments. Both AEGL-2 and -3 values are based on a single rat study by Terrill et al. (1989). The AEGL-2 values were based on the threshold value for respiratory symptoms with an interspecies UF of 10, and intraspecies UF of 3, and a modifying factor of 3 because of the limited data. The AEGL-3 was based on the NOEL for mortality with the same UFs. The NAC/AEGL committee discussed the suggestions proposed by the Michigan DEQ, but felt that the present total UFs of 100 for each AEGL value were adequate and that AEGL-2 values are not usually set on the basis of a NOEL. A motion was made by Mark McClanahan to elevate the chemical from proposed to interim status. It was seconded by Steve Barbee. The motion was approved unanimously by the NAC/AEGL (Appendix N).

TETRACHLOROETHYLENE:

Two *Federal Register Notice* responses were received. They are from the Michigan Department of Environmental Quality (MDEQ) (Attachment 17, Comment No. 2), and John Morawetz (Attachment 19).

MDEQ noted that human data are preferred in the development of AEGLs. They question the accuracy /precision of the measured values when taking into account the descriptions of the exposure estimates in the Rowe and Carpenter studies. It was suggested that an UF be added for the adequacy of the data. MDEQ also questioned the reduction in the interspecies UF to 3 based on rodents and humans experiencing similar effects when exposed to CNS depressants. MDEQ thought this reasonable for the pharmacodynamics, but that the pharmacokinetic portion of the

uncertainty factor was not adequately addressed. Statements were also made that the summary noted no developmental anomalies, while the text describes some adverse effects in offspring. Lastly, they also questioned whether positive carcinogenicity data is considered in the derivation of AEGLs.

John Morawetz raised a concern regarding the AEGL-2 values recommended by the AEGL committee for tetrachloroethylene. He felt that the Rowe study supported by the Stewart (1961) study had indications that deserve greater weight in setting the AEGL-2 values. He also requested that the Committee reconsider and lower the current recommended AEGL-2 levels. An alternative proposal would be to start with the 600 ppm for 10 minutes and use an uncertainty factor of 3 for human variability.

Reply: Chemical manager, Bill Bress, responded to the comments. First, the NAC/AEGL addressed the comments from John Morawetz. The NAC/AEGL noted that the Rowe study has indications that should be considered in setting the AEGL-2. It was decided to set the 10- and 30-minute AEGL-2 values equal to the 1-hour AEGL-2 value of 230 ppm because the Rowe et al. (1952) study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort). After applying an uncertainty factor of 3 for intraspecies variation, the AEGL values based upon this study are consistent with the 1-hour AEGL-2 value of 230 ppm.

With regard to the state of Michigan, it was felt by the NAC/AEGL that the UFs applied were adequate. With regard to reproductive effects, the NAC/AEGL considered the lack of an increase in litter effects as a lack of reproductive effects. With regard to positive cancer data, Robert Benson will provide a slope factor for tetrachloroethylene, and an appendix with numbers based on cancer as the endpoint of concern will be added to the TSD.

A motion was made by Robert Benson and seconded by John Morawetz to elevate the chemical from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix O).

ALLYL ALCOHOL

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 3). MDEQ made two comments. The first comment was that the values set for AEGL-1 were constraining to the setting of the AEGL-2 and -3. The second comment was that the TLV was 0.5 ppm while the AEGL-1 value was 1.8 ppm.

Reply: AEGL values are set independently of other guidelines depending on the values and effects found in the data. The second comment was replied to by noting that the NAC/AEGL did have a rational discussion on this topic. It was noted that the TLV of 0.5 ppm is an 8 hr per day exposure for the lifetime of the working individual while the 1.8 ppm AEGL value is for a single,

acute exposure. The AEGL value is different than the TLV based on the length of time of the exposure as well as who the value is intended to protect.

A motioned was made by John Morawetz and seconded by Mark McClanahan to uphold the current AEGL values. The motion was approved by the NAC/AEGL (YES: 22; NO:1; Abstain: 0) (Appendix P).

Additional comment was made during the NAC/AEGL meeting by Will Bell from Lyondale manufacturing who noted that the committee did a very good job in preparing the document.

AGENTS GA, GB, GD, GF, VX

A total of four sets of comments from the FR notice (66FR21940; May 2, 2001) of proposed AEGL values for the nerve agents GA, GB, GD, GF and VX were received. They are:

1. Monty Herr of the Lawrence Livermore National Laboratory (LLNL; Attachment 19)
2. Christopher Bittner of the Utah Dept. of Environmental Quality, Division of Solid and Hazardous Waste (UT DEQ; Attachment 20)
3. Paul Joe of the Centers for Disease Control and Prevention, Chemical Demilitarization Branch (DHHS/CDC; Attachment 21)
4. LTC Paula Lantzer, Product Manager of the U.S. Army Soldier and Biological Chemical Command, Chemical Stockpile Emergency Preparedness Program (USA SBCCOM/CSEPP; Attachment 22).

An overall summary of the FR comment responses was presented by Annetta Watson (Attachment 23) during the NAC/AEGL meeting. For brevity in the meeting highlights, a summary of the principal remarks made by each commentor and the corresponding NAC/AEGL replies are provided below. Each original FR comment on nerve agents is presented in Attachments 19-22, and is accompanied by detailed NAC/AEGL replies in **bold face** font.

Summary of Commentor No.1 Remarks: Monty Herr suggested a number of alternative values for UFs, including inclusion of an additional MF for an incomplete agent-specific database for nerve agents GA, GD and GF in comparison to the database for agent GB as well as noting that selection of SFEMG changes as a protective definition of AEGL-2 effects suggests that an Intraspecies UF < 10 is warranted. In addition, Dr. Herr provided additional source citations of technical and memo reports from Defense Research Establishment Suffield (Canada) and TNO Prins Maurits Laboratory, The Netherlands; and made a number of editorial suggestions regarding word selections, expanded treatment of certain source material, and alternate explanations of experimental observations.

Reply to Commentor No.1 by NAC/AEGL (Attachment 19): The database for G-agents as a group is considered complete in that

- experimental data are available for multiple species, including human (non-lethal)
- documented non-lethal and lethal endpoints exhibiting exposure-response data

- known mechanism of toxicity; all endpoints represent response continuum to anticholinesterase exposure
- there are no uncertainties regarding reproductive/developmental effects, or carcinogenicity

Since the mechanism of action is the same (cholinesterase inhibition), data uncertainty is reduced, and target organ effects are similar but differ in magnitude. The database for agent VX is considered much less complete than the composite database for G-series agents; thus, application of MF = 3 for agent VX is warranted and consistency in logic is maintained.

The NAC/AEGL had considered an intraspecies UF<10 for determination of the AEGL-2 for agent GB, but this option was previously rejected by a NAC/AEGL majority in favor of a UF = 10.

The additional citations are accepted with thanks and will be incorporated into the next edition of the TSD as summarized in a new report currently in press by DRES in Alberta, Canada. If analyses of these new experimental data indicate any need for a change in values of any nerve agent AEGL estimate, the document developer will return to the NAC/AEGL for further consideration.

It is further noted that the primary VX concern of the Office of the Army Surgeon General is focused on VX vapor rather than VX aerosol; a footnote will be added to each VX AEGL table pointing out that the AEGL estimates for agent VX are for vapor exposure only. All necessary editorial corrections will be made, and new reference material identified by Dr. Herr will be incorporated in an appropriate manner.

Summary of Commentor No. 2 Remarks: Christopher Bittner communicated an overall concern that a single relative potency factor ("of 10") comparing agent VX to agent GB was, in his opinion, not supported by information presented in Tables of the VX TSD and that the "relative potency should be derived based on the experimental data that match...exposure regime and toxicological endpoint." The Commentor further remarked that, in his opinion, the estimate of n=2 is not based on VX-specific data, and that the MF should be equal to10 and not 3.

Reply to Commentor No. 2 by NAC/AEGL (Attachment 20): For Agent VX, there are insufficient valid experimental data that match the needed "...exposure regime and toxicological endpoint." The TSD makes this finding very clear.

The NAC/AEGL and commentor are in agreement on the need for more and better data characterizing VX vapor toxicity. As a consequence, the

- NAC/AEGL identified research studies specifically designed to reduce uncertainties in estimates
- NAC/AEGL declared VX AEGL estimates "temporary" and subject to re-evaluation in 3 years
- NAC/AEGL acknowledged existing data gaps and made practical suggestions for collection of specific new data to elucidate dose-response curves and determination of "n"

Until additional data from well-conducted experimental studies are available, current assumptions and value of "n" (=2) are reasonable, are supported by existing experimental data, and meet requirements of the SOPs. The fact that these AEGL estimates for Agent VX are considered **Temporary** by the NAC/AEGL will be more highly emphasized in the next edition of the TSD for presentation to the COT.

Further, the Commentor is considering the range of relative potency ratios cited in Tables of Agent VX TSD without making any distinction between primary (text boldface) and secondary sources. NAC/AEGL SOPs require use of primary source data for AEGL derivations; verifiable EXPERIMENTAL data for humans, rats and rabbits provide a less variable range of ratios (range = 4.2 to 33). The NAC/AEGL determined that the Commentor's remarks were made without complete knowledge of the content of the NAC/AEGL SOPs, which were published in May, 2001. Until additional data from well-conducted experimental studies are available, the current relative potency approach (RP = 12) is reasonable, is supported by existing experimental data, and meets requirements of the SOPs.

Use of the full default value of 10 for the MF is reserved for cases where there are truly no data; that is the purpose of a default. In the case of agent VX, despite the acknowledged database limitations, much is known about the agent mechanism of action, and comparative experimental data exist for humans as well as the rat and rabbit. In the presence of limited data, the NAC/AEGL considers use of a MF of 3 to be appropriate at this time.

All necessary editorial corrections pointed out by the Commentor will be made.

Summary of Commentor No. 3 Remarks: There is no issue of disagreement. The CDC Chemical Demilitarization Branch is supportive of the NAC/AEGL effort, and wished to inform the NAC/AEGL that the Branch is presently involved in a related area–that of developing long-term occupational and general public exposure guidelines for airborne chemical warfare agents. Further, the Branch wished to state that they could benefit from being made aware of any additional research or insight identified in the FR comment process and requested communication of same from the NAC/AEGL.

Reply to Commentor No. 3 by NAC/AEGL (Attachment 21): The NAC/AEGL welcomes dialogue with the Chemical Demilitarization Branch of the National Center for Environmental Health, CDC, and will be pleased to share information and analyses with the Branch on a continuing basis.

Further, Dr. Mark McClanahan, NAC/AEGL member and staff scientist at the National Center for Environmental Health, CDC, made personal contact with Dr. Joe prior to NAC/AEGL-21 and communicated the NAC/AEGL's wish to continue dialogue.

Summary of Commentor No.4 Remarks: The complete statement of this Commentor's remark is presented below:

"As the Army proponent for emergency planning criteria for the U.S. stockpiled chemical warfare agents, I have coordinated an Army review of the specified AEGLs for G-series and VX nerve agents, and concur with the stated values."

Reply to Commentor No. 4 by NAC/AEGL: The comment provided by LTC Paula Lantzer represents official concurrence by the proponent US Department of the Army agency that originally commissioned development of AEGL estimates for the nerve agents. The NAC/AEGL welcomes this statement of official concurrence and its incorporation into the FR comment process.

Following summarization of the FR comments and replies, the NAC/AEGL Chair George Rusch invited comment by the NAC/AEGL guests, Boris Filatov and Vladimir Tchernov, Director and Assistant Director, respectively, of the South Center for Chemical Emergencies (Volgograd Research Institute of Hygiene, Toxicology and Occupational Pathology, Volgograd, Russia). Dr. Filatov counseled that it was important to develop planning estimates for use in potential emergencies given that the chemical munitions in storage in both the USA and Russia were aging and deteriorating. Boris Filatov encouraged the NAC/AEGL process and members in their efforts to develop appropriate estimates, and welcomed the opportunity to review the draft nerve agent TSDs as a means of collaboration in the NAC/AEGL process for these compounds of mutual international importance.

At the close of discussion, Bill Bress moved that the status of the AEGL estimates for nerve agents GA, GB, GD, GF and VX be elevated from "proposed" to "interim." Bill amended this motion to include the proviso that the document developer return to the NAC/AEGL if evaluation of any new information indicated any need for change in the AEGL estimates. The amended motion was seconded by Glenn Leach. The motion was carried (YES: 19; NO: 2; ABSTAIN; 0) (see Attachment Q).

ACRYLIC ACID

Two responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 1) and The Acrylic Monomer Manufacturers, Inc. (Attachment 24). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

PHENOL

Two responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 4) and The American Chemistry Council's Phenol Regulatory Panel (Attachment 25). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

METHANOL

Three responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 5), the Methanol Institute (Attachment 26) and John Morawetz (Attachment 27). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

The meeting highlights were prepared by Hanks Spencer and Po-Yung Lu , Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

Attachment 1. Meeting Agenda
Attachment 2. List of Attendees
Attachment 3. Data Analysis of Boron Trifluoride
Attachment 4. Data Analysis of Chlorine Dioxide
Attachment 5. Data Analysis of N,N-Dimethyl Formamide
Attachment 6. Clarification of AEGL-1 values of Hydrogen Cyanide
Attachment 7. Federal Register Notice Comments and Data Analysis of Phosgene
Attachment 8. Re-evaluation of Xylenes
Attachment 9. PBPK Modeling Extrapolation for Xylenes
Attachment 10. Monitoring Charts on H_2S from Texas
Attachment 11. Q&A Posed by NAC/AEGL Committee Members
Attachment 12. Use of RD50 data for Development of AEGLs by Larry Gephart
Attachment 13. Application of ASTM Standard Method E981-84 to "The Comparative and Qualitative Characterization of JP-8's Potential for Respiratory Irritation" by John Hinz
Attachment 14. The Relative Susceptibility of Childhood Asthmatics and Adult Asthmatics to Acute Exposures of Irritant Chemicals
Attachment 15. Handout on KAIF System
Attachment 16. *Federal Register* Comments of Perchloromethyl Mercaptan from Tomen Agro, Inc. by Scott A. Mobley
Attachment 17. *Federal Register* Comments of Acrylic acid, Tetrachloroethylene, Ally Alcohol, Phenol, Methanol, Tetranitromethane, Toluene, and Furan from Mary Lee Hultin, Michigan Department of Environmental Quality.
Attachment 18. *Federal Register* Comments of Tetrachloroethylene by John Morawetz
Attachment 19. *Federal Register* Comments on G-agents and Agent-VX from LLNL by Monty L Herr
Attachment 20. *Federal Register* Comments on Nerve agent VX from Utah Division of Solid and Hazardous Waste by Christopher Bittner
Attachment 21. *Federal Register* Comments on Nerve agents from Chemical Demilitarization Branch of CDC by Paul Joe
Attachment 22. *Federal Register* Comments on TSDs of Nerve agents from US Army, LTC Paula Lantzer
Attachment 23. Summary of overall *Federal Register* Comments on proposed nerve agent AEGL estimates by Annetta Watson
Attachment 24. *Federal Register* Comments of Acrylic acid from The Acrylic Monomer Manufacturers, Inc.
Attachment 25. *Federal Register* Comments of Phenol from American Chemistry Council
Attachment 26. *Federal Register* Comments of Methanol from Methanol Institute
Attachment 27. *Federal Register* Comments of Methanol from John Morawetz

LIST OF APPENDICES

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-21
June 11-13, 2001

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D. C.

AGENDA

Monday, June 11, 2001

10:00 AM	Introductory remarks and approval of NAC/AEGL-20 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	NAS/AEGL review status & international matters (Roger Garrett)
10:30	Issue of child asthmatics vs. adult asthmatics (Ernie Falke)
11:15	Consideration of odor in AEGL-1 development (Macel van Raaij)
12:00 PM	Lunch
1:00	Review of Boron trifluoride (George Rusch/Claudia Troxel)
3:00	Break
3:15	Review of Phosgene: *Federal Register* comments (Bill Bress/Cheryl Bast)
4:15	Review of Xylenes - PBPK modeling (Loren Koller/Claudia Troxel)
5:15	Administrative matters
5:30	Adjourn for the day

Tuesday, June 12, 2001

8:00 AM	Use of RD_{50} data for development of AEGLs (Larry Gephart and John Hinz)
9:00	Review of Chlorine dioxide (Bob Benson/Cheryl Bast)
10:15	Break
10:30	Review of Chlorine dioxide (continued)
11:30	Lunch
12:30 PM	Review of N,N-Dimethylformamide (Loren Koller/Claudia Troxel)
2:30	Break
2:45	Review of Hydrogen sulfide: AEGL-1 (Steve Barbee/Cheryl Bast)
4:15	Review of comments received from May 2, 2001, *Federal Register Notice*
5:30	Adjourn for the day

Wednesday, June 13, 2001

8:00 AM	Review of comments received from May 2, 2001, *Federal Register Notice* (continued)
10:30	Break
10:45	Overview of South Center for Chemical Emergencies Institute of Hygiene, Toxicology and Occupational Pathology Volgograd, Russia (Boris Filatov)
12:30 PM	Adjourn meeting

NAC AEGL - 21

Attachment 2

June 11-13, 2001

Name	Affiliation	Phone #
Po-Zyung Lu	ORNL	(865) 574-7587
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—OVER—

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Chris Van Beever	Arch Coal, Inc	314-994-2921
Claudia M Tirpak	ORNL	(307)332-1555
Sherri Clark	American Chemistry Council	703-741-5619
Stephanie Willett	EPA/OEI	202-260-6001
Annette P. Watson	ORNL	865-576-2125

Erin Wise CHPPM 410-436-2714

Veronique Hauschild CHPPM (US Army) 410-436-5213

BORON TRIFLUORIDE:DIMETHYL ETHER

- One of several complexes formed with boron trifluoride for ease of handling BF_3. Ether complexes consist of 1:1 molar ratio of BF_3 and the dimethyl or diethyl ether; can dissociate under proper temperature/ pressure conditions.
- Only one study addressed toxicity of BF_3:dimethyl ether - only nominal concentrations.
- Because complex can dissociate to form BF_3, the AEGL derivations are based upon this one chemical species alone.

BORON TRIFLUORIDE (BF_3)

- Colorless gas - pungent suffocating odor
- Gas is stable in dry air, but immediately forms dense white cloud when exposed to moist air; upon exposure to even low levels of moisture in air, BF_3 reacts to form dihydrate, BF_3:$2H_20$. BF_3 dihydrate is strongly corrosive to the eyes and skin
- Excellent catalyst; has fire retardant and antioxidant properties, nuclear applications, and insecticidal properties
- Toxicity Data:
  - Human: odor detection
  - Animal: acute toxicity data available in dogs, rats, mice, and guinea pigs, but exposure conc. generally expressed as nominal conc.
- Effects of exposure in animals:
  - short-term exposures - pulmonary irritation
  - repeated exposures - pulmonary irritation and/or renal toxicity

TOXICITY DATA

- Human: conc. of 1.5 ppm [4.1 mg/m^3] described by worker as having a "rather pleasant acidic odor," indicating that the odor threshold had been reached. Although the worker noted the smell of BF_3 to be pleasant, it is likely that others would find the odor unpleasant.

- Animal - two studies reporting measured concentrations: Rusch et al., 1986 and Torkelson et al., 1961

  These 2 studies measured the exposure conc. and compared them to nominal conc.; found actual conc. ranged from 25-56% of nominal

Rusch et al. 1986: Exposures to BF_3 dihydrate aerosol

ACUTE:

- Groups of 5, F344 rats/sex exposed for 4 hours to 0, 1010, 1220, 1320, or 1540 mg/m^3
- Clinical signs during and/or after exposure:
  ↓ activity, closed eyes, excessive lacrimation, oral/nasal discharge, gasping, moist/dry rales,
- Wt loss; followed by wt gain by 14 days post exp.
- Mortality:

Conc.	Mortality	Day of death
0	0/10	-
1010	3/10	0, 3, 6
1220	2/10	0, 3
1320	8/10	1,1,2,3,3,3,4,5
1540	9/10	0,0,0,1,2,3,4,5,5

- 4-hr LC_{50}: 1200 mg/m^3

- Red discoloration of lungs in several animals from all exposure groups

2-WEEK STUDY:

- Groups of 5 F344 rats/sex exposed for 6 h/d, 5 d/wk for 2 wk, to 0, 24, 66, or 180 mg/m^3
- Clinical signs during and/or after exposure: oral/nasal discharge, lacrimation, dry/moist rales, gasping, ano-genital staining, poor condition
- All 10 high-conc. rats died by 6th exposure
- Wt loss in all exp. male groups and mid-and high-conc. females; followed by wt gain by 14 d post exp.
- Concentration-related ↑ in lung wt.
- At 180 mg/m^3, necrosis and pyknosis of proximal tubular epithelium in kidneys

SUBCHRONIC (13 -weeks):

- Groups of 20 F344 rats/sex exposed for 6 h/d, 5 d/wk for 13 wk, to 0, 2, 6, or 17 mg/m^3
- Clinical signs during and/or after exposure: ↑dried red material around nose and mouth, lacrimation, and dry rales (1° high-conc. group)
- One high-conc. male rat died at wk 12
- No changes in body wt, ophthalmological findings, hematology analysis, organ wt, gross necropsy
- Concentration-related ↑ in fluoride levels in femurs
- Toxic renal tubular necrosis seen in high-conc. male rat with ↑ BUN levels and male rat that died early

Torkelson et al., 1961

4 mg/m^3 for 7 h/d, 5 d/wk for 127-128 exp.: No effects (appearance, bw, organ wts, gross necrospy)

- → Rats 12/sex: areas of pneumonitis (slight), peribronchiole round cell infiltration, congestion
- → Guinea pigs 10 /sex: slight pnuemonitis
- → Rabbits 3/sex: no effects

8-11 mg/m^3 for 7 h/d, 5 d/wk:

- → Rats- 5 Fe; exposed 33 times: normal in appearance and growth, ↑fluoride in bones and teeth
- → Guinea pigs- 10 M; 4 died - deaths accompanied by asthmatic attack; 6 survivors exhibited breathing difficulty - exposed 29

35 mg/m^3 (nominal) for 7 h/d:

- → Rats- 14 Fe; 1 rat died but cause undetermined; survivors: no effects on appearance or organ wt, chemical irritation of lungs - pnuemonitis
- → Guinea pigs - 10 M; 7 died from respiratory failure or asphyxiation after 19th exp - ↑ lung wts, pneumonitis

AEGL-1 Derivation

Key study: Torkelson et al., 1961

Effects:
Worker noted conc. of 1.5 ppm [4.1 mg/m^3] BF_3 to have "rather pleasant acidic odor," indicating odor threshold reached. Although worker noted smell of BF_3 to be pleasant, it is likely others would find odor unpleasant.

Uncertainty factors: 1
Interspecies UF: 1
Intraspecies UF: 1 odor not irritating at this level

Time scaling: Value set equal to all time periods

AEGL-1 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	30-min	1-hr	4-hr	8-hr
4.1	4.1	4.1	4.1	4.1

Level appears to approach threshold for irritant effects: minimal signs of irritation noted in rats exposed to 2 or 6 mg/m^3 for 6 h/d, 5 d/wk for 13 wk. (Rusch et al., 1986)

AEGL-2 Derivation

AEGL-3 levels ÷ 3 to obtain an estimate of AEGL-2:

- Data meeting definition of AEGL-2 endpoint not available
- Dose-response curve for lethality was steep (Rusch et al, 1986)

AEGL-2 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	30-min	1-hr	4-hr	8-hr
27	27	21	13	6.7

AEGL-2 based on the Rusch et al. (1986) 2-week study:
- Apply same UF (30) and time extrapolation as for AEGL-3; set 10-min value equal to 30-min value
- One obtains the following values:
  5.0, 5.0, 4.0, 2.5, and 1.7 mg/m^3, respectively.
- These values inconsistent with existing animal data: exposure of rats, rabbits, and guinea pigs to 4 mg/m^3 for 7 h/d, 5 d/wk for 127-128 exp. resulted in minimal effects (Torkelson et al., 1961).

AEGL-3 Derivation

Key study:
Rusch et al., 1986

Effects:
4-hour LC_{50} of 1200 mg/m^3

Uncertainty factors: 30
Interspecies UF: 10 - species differences exist in sensitivity to BF_3, with the guinea pig being the most sensitive to lethality
Intraspecies UF: 3 - based on evidence that at acute exposures, BF_3 acts as an irritant

Time scaling: Default:
n = 1 for shorter to longer times
n = 3 for longer to shorter times
10-min value set equal to 30-min (4-h exposure)

AEGL-3 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	30-min	1-hr	4-hr	8-hr
80	80	63	40	20

Summary of AEGL Values for BF_3 (mg/m^3)					
Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	4.1	4.1	4.1	4.1	4.1
AEGL-2	27	27	21	13	6.7
AEGL-3	80	80	63	40	20

Attachment 4

ACUTE EXPOSURE GUIDELINE LEVELS FOR

CHLORINE DIOXIDE

NAC/AEGL-21
June 11-13, 2001

Chemical Manager: Robert Benson
ORNL Staff Scientist: Cheryl Bast

AEGL-1 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**0.10 [0.30]**	**0.10 [0.30]**	**0.10 [0.30]**	**0.10 [0.30]**	**0.10 [0.30]**

Species: Rat
Concentration: 0.1 ppm
Time: 5 hours/day for 10 weeks
Endpoint: No effects
Reference: Dalhamn, 1957

Time Scaling: None. Values were held constant across all time points

Interspecies UF = none
Intraspecies UF = none

No UFs were applied since the 0.1 ppm concentration is a no-effect-level from a 10-week repeated-exposure study.

AEGL-2 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-2	**1.8 [5.0]**	**1.3 [3.6]**	**1.0 [2.8]**	**0.25 [0.69]**	**0.13 [0.36]**

Species: Rabbit & Guinea Pig
Concentration: 10 ppm
Time: 1 hr.
Endpoint: Difficulty Breathing
References: Hecht, 1950

Time Scaling: Default Values

n = 1 (4-hr. & 8-hr.) Or n = 3 (10-min., 30-min., &1-hr.)

Uncertainty Factor: 3 x 3 =10

Interspecies = 3 (More sensitive species used- No effects were observed in similarly exposed rats and mice.)

Intraspecies = 3 (Irritation is unlikely to vary greatly among individuals)

Endpoint chosen is likely less than that defined by AEGL-2; however, it was chosen due to the sparse database.

AEGL-3 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	4.6 [13]	3.2 [8.8]	2.5 [6.9]	1.0 [2.8]	0.50 [1.4]

Species: Rat, Mouse, Rabbit & Guinea Pig
Concentration: 20 ppm
Time: 2 hr.
Endpoint: No Lethality Observed
References: Hecht, 1950

Time Scaling: Default Values

n = 1 (4-hr. & 8-hr.) Or n = 3 (10-min., 30-min., &1-hr.)

Uncertainty Factor: 3 x 3 =10

Interspecies = 3 (No deaths occurred in any of four species tested)

Intraspecies = 3 (Irritation is unlikely to vary greatly among individuals)

Endpoint chosen is likely less than that defined by AEGL-3; however, it was chosen due to the sparse database.

Summary Table of AEGL Values for Chlorine Dioxide [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**0.1 (0.3)**	**0.1 (0.3)**	**0.1 (0.3)**	**0.1 (0.3)**	**0.1 (0.3)**	**NOEL in rats exposed to 0.1 ppm, 5 hr/day, 10 weeks (Dalhamn, 1957)**
AEGL-2 (Disabling)	**1.8 (5.0)**	**1.3 (3.6)**	**1.0 (2.8)**	**0.25 (0.69)**	**0.13 (0.36)**	**Breathing difficulty in guinea pigs and rabbits. 10 ppm. 1 hr. (Hecht, 1950)**
AEGL-3 (Lethal)	**4.6 (13)**	**3.2 (8.8)**	**2.5 (6.9)**	**1.0 (2.8)**	**0.5 (1.4)**	**NOEL for death in rats, mice, guinea pigs and rabbits. 20 ppm. 2 hr. (Hecht, 1950)**

ACGIH TLV-TWA: **0.1 ppm**
ACGIH TLV-STEL: **0.3 ppm (skin notation)**

NIOSH IDLH: **5 ppm**
NIOSH REL: **0.1 ppm**
NIOSH STEL: **0.3 ppm**

OSHA PEL: **0.1 ppm**

MAK (German): **0.1 ppm**
MAC (Dutch): **0.1 ppm**

DIMETHYL FORMAMIDE (DMF)

- Clear to slightly yellow liquid
- Produced from reacting dimethylamine in methanol with carbon dioxide in presence of sodium methylate
- American manufacturers use DMF as a solvent; consumed 32 million pounds in 1993
- Primary end-users are manufacturers of: pharmaceuticals, electronic components, butadiene, urethanes
- Odor threshold: 0.47 to 100 ppm; faint amine (fishy) odor
- Effects of exposure
  - gastrointestinal disturbances
  - disulfiram-like symptoms with concomitant alcohol consumption
  - liver toxicity

1

METABOLISM, DISPOSITION, MECHANISM

- Pulmonary retention of DMF ~ 90% in volunteers exposed to 3, 10 or 20 ppm DMF for 8 h
- In rats, distribution of DMF and metabolites fairly uniform among blood, liver, kidney, brain, and adrenals following 4-h exp. to 565 or 2250 ppm
- DMF is primarily metabolized by CYP 2E1 in rats and humans; hyroxylation of its methyl groups to form HMMF, NMF, formamide; high concentrations of DMF can inhibit its metabolism
- Also, formyl group can be oxidized to an as of yet unidentified reactive intermediate(s), resulting in generation of toxic lesion (proposed mechanism of toxicity) or in conjugation with GSH to form SMG and urinary metabolite AMCC
- Excretion of DMF and its metabolites occurs almost exclusively via the urine, and elimination of these metabolites occurs rapidly in humans.

2

AEGL-1 Derivation

Key study: Kimmerle and Eben, 1975b

Effects:
1 female, 3 male volunteers exposed to 87 ppm for 4 h to assess metabolism. If effects present, mild enough to not interfere with exposure.

Uncertainty factors: 10
Interspecies UF: 1
Intraspecies UF: 10 for differences in CYP 2E1 levels (induced by alcohol); also detoxification of reactive intermediate by conjugation with GSH, levels can become depleted

Time scaling: Default:
n = 1 for shorter to longer times
n = 3 for longer to shorter times
10-min value set equal to 30-min (4-h exposure)

AEGL-1 Values for DMF (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
17	17	14	8.7	4.3

3

AEGL-1

Other controlled human exposures:

Summary of controlled human exposures to DMF			
Number of subjects	Duration (h)	Conc. (ppm)	Reference
10 (5 M, 5 Fe)	8	3	Mraz and Nahova, 1992
		10	
		20	
10 (5 M, 5 Fe)	8	20	Mraz et al., 1989
4	4	26	Kimmerle and Eben, 1975b
		87	
4	2	82	Eben and Kimmerle, 1976

All of these studies designed to assess metabolism. If effects present, mild enough to not interfere with exposure. While the fact that adverse effects were not reported does not necessarily mean that none were noted by the subjects, if effects were present they were not so uncomfortable that they caused a discontinuation of the exposure.

4

AEGL-2 Derivation

Data meeting the definition of an AEGL-2 endpoint were not available. Therefore, AEGL-3 levels divided by 3 to provide an estimate.

AEGL-2 Values for DMF (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
110	73	60	37	25

AEGL-2

AEGL-2 values supported by:

- Values derived if using a study with health effects below the definition of an AEGL-2 endpoint:
  - Roure et al. (1996) reported that rats exposed to 991 ppm DMF for 4 hours exhibited 140-fold increase in sorbitol dehydrogenase levels and 130-fold increase in glutamate dehydrogenase levels
- Apply the same UF as used for AEGL-3 and same time extrapolation. 10-min value set equal to 30-min value because exposure was for 4 hours

AEGL-2 Values for DMF (ppm)					
	10-min	30-min	1-hr	4-hr	8-hr
Proposed	110	73	60	37	25
Supporting	66	66	52	33	23

AEGL-3 Derivation

Key study:
MacDonald, 1982

Effects: Groups of 3 male and 3 female Wistar rats
1- or 3-h exposure to 3700 ppm - no mortality
7-h exposure to 3700 ppm - killed 2/3 M; 3/3 Fe

Uncertainty factors: 30
Interspecies UF: 3: Mechanism of toxicity related to metabolism of DMF; evidence indicates that primary enzyme responsible for metabolism (P450 2E1) is similar in rats and humans. Although mechanism not yet been clearly defined, limited species differences have been identified in manifestation of toxicity. Documented occupational exposures in humans demonstrate similar hepatic effects as those seen in animals (cats, mice, rats) following repeated exposure to DMF. Indices of liver toxicity range from elevated serum enzymes to histopathological findings of hepatic degeneration and necrosis.
Intraspecies UF: 10 for differences in CYP 2E1 levels (induced by alcohol); also detoxification of reactive intermediate by conjugation with GSH, levels can become depleted.

Time scaling:
Value of n not empirically derived because inadequate data; therefore default value of n should be used in the temporal scaling of AEGL values across time. However, if one applies the default value of $n = 1$ for extrapolating from shorter to longer exposure periods, one obtains a 4-h value of 93 ppm and an 8 hour value of 46 ppm. Going with a default value results in AEGL values that are inconsistent with the available human data used for derivation of AEGL-1 (87 ppm for 4 h). The AEGL-1 values help to serve as a baseline: they are based on human exposure data at which no adverse effects were reported. Therefore, in the absence of any further data, an n of 2 was selected as compromise between the possible values for n: it is between n=1 (which results in unreasonable values) and an n=3, a less conservative value. AEGL-3 values are therefore derived using an n=3 for extrapolation to 10 and 30 min and 1 h, and an n=2 for extrapolation to 4 or 8 h.

AEGL-3 Values for DMF (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
320	220	180	110	76

Summary of AEGL Values for DMF (ppm)					
Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	17 ppm 51 mg/m³	17 ppm 51 mg/m³	14 ppm 42 mg/m³	8.7 ppm 26 mg/m³	4.3 ppm 13 mg/m³
AEGL-2	110 ppm 330 mg/m³	73 ppm 220 mg/m³	60 ppm 180 mg/m³	37 ppm 110 mg/m³	25 ppm 75 mg/m³
AEGL-3	320 ppm 960 mg/m³	220 ppm 660 mg/m³	180 ppm 540 mg/m³	110 ppm 330 mg/m³	76 ppm 230 mg/m³

Summary of Lethal Inhalation Data in Laboratory Animals			
Conc. (ppm)	Duration	Effect	Reference
Rat			
5000	4 or 8 h	No mortality (within 24 h)	Lundberg et al., 1986
3700 nominal	1, 3 h	3/3 males and 3/3 females survived; signs: excessive grooming;	MacDonald, 1982
	7h	2/3 males and 3/3 females died; signs: excessive grooming, lethargy	
2523	6 h/d for 5 d	8/10 died; 7- acute liver necrosis; 1- acute pulmonary edema and congestion signs: progressive weakness, discomfort, weight loss	Kennedy and Sherman, 1986
1200	6 h/d, 5d/wk, for 12 wk	1 male and 1 female died: liver necrosis surviving rats: increased cholesterol; decreased b.w.; liver necrosis and nuclear size and cytoplasmic variations	Craig et al., 1984
Mouse			
3981	2 h	LC_{50}	Stasenkova, 1961
670		highest no-effect level for mortality	

Summary of Nonlethal Inhalation Data in Laboratory Animals *			
Conc. (ppm)	Duration	Effect	Reference
Monkey			
500	6 h/d, 5 d/wk; 2 wk	no effects (clinical signs, hematology, clinical chemistry)	Hurtt et al., 1991
500	6 h/d, 5 d/wk; 13 wk	no effects (clinical signs, b.w., hematology, clinical chemistry, urinalysis, semen, gross necropsy)	Hurtt et al., 1992
Rat			
5000	4 or 8 h	no mortality (within 24 h)	Lundberg et al., 1986
280	4 h	↑SDH 20 h post exposure	Lundberg et al., 1986
560		↑SDH 20 h post exposure	
2250		SDH not affected 20 h post exposure no histological hepatic changes	
153	4 h	24 h post exp:↑ SDH (2-fold)	Roure et al., 1996
313		24 h post exp:↑ SDH and GLDH (6-fold)	
441		24 h post exp:↑ SDH and GLDH (10.5-fold) at 72 h post exp -only GLDH ↑1.5 fold	
991		48 h post exp:↑ SDH (140-fold); GLDH (130-fold) at 72 h post exp: only GLDH 120-fold	
126, 281, 314	4 h	↑ GLDH: + 38%, +516%, +260%, respectively ↑ GPT: +37%, +54%, +50%, respectively ↑ SDH: +130%, +325%, +379%, respectively	Brondeau et al., 1983
400, 800	6 h/d, 5 d/wk; 13 wk	on exposure day 4: elevated ALT, SDH, isocitrate dehydrogenase, bile salts	NTP, 1992
Mouse			
1628, 2110	10 min	respiratory rate decrease of 12.8% and 28.3%, respectively; RD_{50} could not be determined	Kennedy and Sherman, 1986
Cat			
100, 230, 450	8 h/d, 6 d/wk for 120 days	poor appetite, wt loss no effects on clinical signs, blood analysis, urinalysis, ECG recordings necropsy: fatty degeneration - no necrosis	Massman, 1956

Version 1: HYDROGEN CYANIDE AEGL- 1

George Rodgers indicated the need to evaluate the data for only the AEGL-1 values (Attachment 12). Values were based on the Leeser et al. (1990) study; however, as pointed out by John Morawetz, the geometric mean values for all job categories of the study were <1 ppm (Attachment 13). No clear exposure-related symptoms were reported. The manner in which the data were reported in the study made interpretation of some of the results difficult. Two other studies were also available for evaluationEl Ghawabi et al. (1975) and Grabois (1954). Committee comments included letting the approved values in July stand (values in ascending time order from 10 minutes to 8 hours of 2.5, 2.5, 2.0, 1.3, and 1.0 ppm, respectively), but adding more detailed comments on the sampling methods, in particular emphasizing personal monitoring (TWA samples) over short-term or area samples. It was suggested that additional details on sampling be added to the SOPs. Chairperson Ernie Falke asked for a show of hands to accept the values as passed in July and only clarify the rationale for the values. The show of hands was unanimous. No written ballot was made.

Version 2: HYDROGEN CYANIDE AEGL- 1

George Rodgers indicated the need to evaluate the data for only the AEGL-1 values (Attachment 12). Values were based on the Leeser et al. (1990) study; however, as pointed out by John Morawetz, the study is unclear at what exposure level the lack of health effects can be attributed to. The health effects are reported as aggregated for all workers in 8 job titles while the exposures are reported for each of 8 job titles (6 of the 8 job titles had geometric mean values at or below 0.5 ppm, one job title had a mean value of 1 ppm) (Attachment 13). **The committee agreed that although the Lesser study generally supported our values, it can not be used as the primary study for AEGL-1 determination.** Two other studies were also available for evaluation. El Ghawabi et al. (1975) and Grabois (1954). Committee comments included letting the approved values in July stand (values in ascending time order from 10 minutes to 8 hours of 2.5, 2.5, 2.0, 1.3, and 1.0 ppm, respectively), but adding more detailed comments on the sampling methods, in particular emphasizing personal monitoring (TWA samples) over short-term or area samples. It was suggested that additional details on sampling be added to the SOPs. George Rusch (Chair) had to meet a previously scheduled commitment and to facilitate completion of discussion of this chemical George appointed Ernie Falke to preside in his stead. Chairperson Ernie Falke asked for a show of hands to accept the values as passed in July and only clarify the rationale for the values. The show of hands was unanimous. No written ballot was made.

Version 3: HYDROGEN CYANIDE AEGL- 1

Approved by NAC/AEGL

George Rodgers indicated the need to evaluate the data for only the AEGL-1 values (Attachment 12). Values were based on the Leeser et al. (1990) study; however, as pointed out by John Morawetz, the study is unclear at what exposure level the lack of health effects can be attributed to. The health effects are reported as aggregated for all workers in 8 job titles while the exposures are reported for each of 8 job titles (6 of the 8 job titles had geometric mean values at or below 0.5 ppm, one job title had a mean ~~value~~ of 1 ppm) (Attachment 13). **The committee agreed the Leeser study generally supported ~~our~~ values. It is used as a supporting evidence for AEGL-1 values derived from El Ghawabi et al (1975) ~~& Grabois (1954).~~** Two other studies were also available for evaluation El Ghawabi et al. (1975) and Grabois (1954). Committee comments included letting the approved values in July stand (values in ascending time order from 10 minutes to 8 hours of 2.5, 2.5, 2.0, 1.3, and 1.0 ppm, respectively), but adding more detailed comments on the sampling methods, in particular emphasizing personal monitoring (TWA samples) over short-term or area samples. It was suggested that additional details on sampling be added to the SOPs. George Rusch (Chair) had to meet a previously scheduled commitment and to facilitate completion of discussion of this chemical George appointed Ernie Falke to preside in his stead. Chairperson Ernie Falke asked for a show of hands to accept the values as passed in July and only clarify the rationale for the values. The show of hands was unanimous. No written ballot was made.

Attachment 7

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHOSGENE:

DISCUSSION OF FEDERAL REGISTER COMMENTS

NAC/AEGL-21
June 11-13, 2001

Chemical Manager: Bill Bress
ORNL Staff Scientist: Cheryl Bast

January 9, 2001

VIA COURIER

OPPT Document Control Office (DCO)
East Tower Rm. G-099
Waterside Mall, 401 M St., SW
Washington, DC

RE: Docket Control Number OPPTS-00302
Proposed Acute Exposure Guideline Levels (AEGLs) for Phosgene (CAS No. 75-44-5)

Dear Sir or Madam:

The Phosgene Panel (Panel) of the American Chemistry Council submits these comments in response to the AEGL values proposed by the Environmental Protection Agency (EPA), National Advisory Committee (NAC) for AEGLs for Hazardous Substances, 65 Fed. Reg. 77866 (Dec. 13, 2000). The Panel is comprised of BASF Corporation; Bayer Corporation; The Dow Chemical Company; DuPont; GE Plastics; Lyondell Chemical Company; PPG Industries, Inc.; Huntsman/Rubicon, Inc.; Syngenta; and Van DeMark Chemical Company. We support NAC's efforts to address the acute toxicity issues associated with phosgene and we appreciate the opportunity to comment on the proposed AEGL values.

As expressed in our letter of December 5, 1997 (enclosed), the Panel finds the proposed values, in general, to be reasonable. However, it remains the opinion of the Panel that the values suggested in our September 22, 1997 letter (enclosed) and subsequent presentation are equally reasonable and scientifically justified. We reiterate the belief that the use of Haber's Rule (*cxt*) in deriving the 4-hour and 8-hour time points, and the 10x uncertainty factor, results in proposed AEGL values that are more conservative than necessary.

The Panel has not previously had the opportunity to comment on NAC's development of 10-minute AEGL values. The 10-minute AEGL 2 value was said to be based on Diller, 1985 (Archives of Toxicology. 57:184-190), with a note that the normal extrapolation from the 30-minute value would be too close to Diller's reported pulmonary edema in rats. If the extrapolation technique used to develop other AEGL values were used, the 10-minute AEGL 2 would appear to be 1.4 ppm. Diller reported some interstitial edematous changes with a sensitive electron microscopy evaluation of exposures at 2.5 ppm for 20 minutes and 1 ppm after 50

minutes, and apparently also at 0.1 ppm. The author noted that the widening of the pulmonary interstices was "assumed to be indicators of physiologic compensation within the blood-air

barrier." Based on the author's conclusion, we believe that the single exposure effects on the interstitium seen with electron microscopy would not indicate a long lasting effect. The proposed 0.6 ppm 10-minute AEGL 2 value is, therefore, overly conservative and the normal extrapolation procedure to ten minutes should be used.

The 10-minute AEGL 3 value (3.6 ppm) is fairly reasonable. Extrapolating to 10 minutes will not yield a precise guide in any case. The proposed value (3.6 ppm) is consistent with the longer duration AEGL 3 values.

The Panel urges that NAC derive the 10-minute AEGL 2 value using the extrapolation method used to derive values for other time points. With appropriate changes to this 10-minute value, the Panel generally supports the proposed NAC AEGL values and the goal of protecting the health and safety of the general population.

If you have any questions, please contact Dr. Anne LeHuray, Phosgene Panel Manager, at (703) 741-5630 or anne_lehuray@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Enclosures

Summary of Proposed AEGL Values for Phosgene [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
AEGL-2 (Disabling)	**0.60 (2.5)**	**0.60 (2.5)**	**0.30 (1.2)**	**0.08 (0.33)**	**0.04 (0.16)**	**Chemical pneumonia rats (Gross et al., 1965)**
AEGL-3 (Lethal)	**3.6 (15)**	**1.5 (6.2)**	**0.75 (3.1)**	**0.20 (0.82)**	**0.09 (0.34)**	**30-minute or 10-minute no-effect-level for death in rats (Zwart et al., 1990)**

Extant Standards and Guidelines for Phosgene	
ERPG-1	**NA**
ERPG-2	**0.2 ppm**
ERPG-3	**1 ppm**
NIOSH IDLH	**2 ppm**
NIOSH STEL	**2 ppm**
OSHA PEL-TWA	**0.1 ppm**
ACGIH TLV-Ceiling	**0.1 ppm**

EXECUTIVE SUMMARY

Phosgene is a colorless gas at ambient temperature and pressure. Its odor has been described as similar to new-mown hay. Phosgene is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal. The production of dyestuffs, isocyanates, carbonic acid esters (polycarbonates), acid chlorides, insecticides, and pharmaceutical chemicals requires phosgene.

Appropriate data were not available for deriving AEGL-1 values for phosgene.

AEGL-2 values were based on chemical pneumonia in rats (2 ppm for 90 min) (Gross et al., 1965). An uncertainty factor of 3 was applied for interspecies extrapolation since little species variability is observed both with lethal and non lethal endpoints after exposure to phosgene. An uncertainty factor of 3 was applied to account for sensitive human subpopulations since the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals (total UF=10). The 1.5 hour value was then scaled to the 30-minute, 1-, 4-, and 8-hour AEGL exposure periods, using $c^n \times t = k$, where n=1 (Haber's Law) since Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber, 1924). The 30-minute value was also adopted as the 10-minute value since extrapolation would yield a 10-minute AEGL-2 value close to concentrations producing alveolar edema in rats exposed for 10-minutes (Diller et al., 1985) and may not be protective.

The 30-minute, 1-, 4-, and 8-hour AEGL-3 values were based on a 30-minute no-effect-level for death in rats (15 ppm) (Zwart et al., 1990). An uncertainty factor of 3 was applied for interspecies extrapolation since little species variability is observed both with lethal and non lethal endpoints after exposure to phosgene. An uncertainty factor of 3 was applied to account for sensitive human subpopulations since the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals (total UF=10). The value was then scaled to the 1-, 4-, and 8-hour AEGL periods, using $c^n \times t = k$, where n=1 (Haber's Law) since Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber, 1924). The 10-minute AEGL-3 value was based on a 10-minute no-effect-level for death in rats and mice (Zwart et al., 1990). An uncertainty factor of 3 was applied for interspecies extrapolation since little species variability is observed both with lethal and non lethal endpoints after exposure to phosgene. An uncertainty factor of 3 was applied to account for sensitive human subpopulations since the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals (total UF=10).

The calculated values are listed in the table below.

Summary of Proposed AEGL Values for Phosgene [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)	Chemical pneumonia rats (Gross et al., 1965)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)	30-minute or 10-minute no-effect-level for death in rats (Zwart et al., 1990)

References:

Diller, W. F., Bruch, J., and Dehnen, W. 1985. Pulmonary changes in rats following low phosgene exposure. *Archives of Toxicology.* 57: 184-190.

Gross, P., Rinehart, W.E., and Hatch, T. 1965. Chronic pneumonitis caused by phosgene. *Archieves of Environmental Health.* 10: 768-775.

Haber, F.R. 1924. Zur geschichte des gaskrieges [On the history of the gas war]. In: Fuenf Vortraege aus den Jahren 1920-23 [Five lectures from the years 1920-1923]. Berlin, Germany: Verlag von Julius Springer; pp. 76-92.

Zwart, A., Arts, J.H.E., Klokman-Houweling, J.M., and Schoen, E.D. 1990. Determination of concentration-time-mortality relationships to replace LC50 values. *Inhalation Toxicology.* 2: 105-117. November 1977.

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHOSGENE DERIVATION SUMMARY

AEGL-1 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
NA	**NA**	**NA**	**NA**	**NA**
Key Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: NA				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Confidence and Support for AEGL values: Data were insufficient for derivation of AEGL-1 values for phosgene				

AEGL-2 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
0.60 ppm	**0.60 ppm**	**0.30 ppm**	**0.08 ppm**	**0.04 ppm**

Key Reference: Gross, P., Rinehart, W. E., and Hatch, T. 1965. Chronic pneumonitis caused by phosgene. Arch. Environ. Health. 10: 768-775.

Test Species/Strain/Number: Wistar rats/ 118 males

Exposure Route/Concentrations/Durations: Rats/Inhalation: 0.5 to 4.0 ppm for 5 minutes to 8 hours to give C x T products between 12 and 360 ppm-min (2 ppm for 1.5 hr was determinant for AEGL-2)

Effects: 2 ppm for 1.5 hr: chemical pneumonia; 0.9 ppm for 1 hr: "chronic pneumonitis"

Endpoint/Concentration/Rationale: Rats/2 ppm for 1.5 hour/ chemical pneumonia

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - little species variability is observed with both lethal and nonlethal endpoints in many studies after exposure to phosgene
Intraspecies: 3 - effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 1. Haber's Law (c x t = k) has been shown to be valid for phosgene within certain limits (U.S. EPA, 1986). Haber's Law was originally derived from phosgene data (Haber, 1924). Reported 1.5 hour data point used for AEGL-2 derivation. AEGL values for the 30-minute, 1-, 4-, and 8-hour exposure periods were based on extrapolation from the 1.5 hour value. The 30-minute value is also adopted as the 10-minute value since extrapolation would yield a 10-minute AEGL-2 value close to concentrations producing alveolar edema in rats exposed for 10-min and may not be protective.

Confidence and Support for AEGL values: The database is rich. Confidence is good. The calculated AEGL-2 values are supported by rat studies where exposure of rats to 1 ppm phosgene for 4 hr resulted in severe pulmonary edema and body weight loss. (Franch and Hatch, 1986; Erlich et al., 1989). Use of these data (and application of a total UF = 10) results in supporting AEGL-2 values of 0.8, 0.4, 0.1, and 0.05 ppm for the 30 min, 1 hr, 4 hr, and 8 hr time points, respectively.

AEGL-3 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
3.6 ppm	**1.5 ppm**	**0.75 ppm**	**0.20 ppm**	**0.09 ppm**

Reference: Zwart, A. Et al. 1990. Determination of concentration-time-mortality relationships to replace LC50 values. Inhalation Toxicol. 2: 105-117.

Test Species/Strain/Sex/Number: Wistar rats/ 5 males and 5 females/ concentration

Exposure Route/Concentrations/Durations: Rats/Inhalation: 12, 15, 16, 17, or 24 ppm for 30 minutes (No-effect-level for death of 15 ppm was determinant for AEGL-3)

Effects:

Phosgene	Concentration	Mortality
	12 ppm	0/10
	15 ppm	0/10
	16 ppm	1/10
	17 ppm	5/10
	24 ppm	9/10

Endpoint/Concentration/Rationale: The 30-minute experimental no-effect-level for death (15 ppm) as a threshold for death in rats for the 30-min, 1-, 4-, and 8-hr values. The 10-min no-effect-level for death of 36 ppm was utilized for the 10-min. value.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - little species variability is observed with both lethal and nonlethal endpoints in many studies after exposure to phosgene
Intraspecies: 3 - effects appear to be due to irritation and binding to macromolecules are not expected to differ greatly among individuals

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 1$. Haber's Law ($c \times t = k$) has been shown to be valid for phosgene within certain limits (U.S. EPA, 1986). Haber's Law was originally derived from phosgene data (Haber, 1924). Reported 30-minute data point used to determine the 30-minute AEGL value. AEGL-3 values for 1-, 4-, and 8-hours were based on extrapolation from the 30 minute value. The 10-min value was based on a reported 10-minute data point.

Confidence and Support for AEGL values: The AEGL-3 values are based on a well-conducted study in rats and the database is rich. Confidence in the data and AEGL values is high.

XYLENES

- Mix of 3 isomers: *meta* (m), *para* (p), *ortho* (o)
- Majority of mixed xylenes produced by catalytic reforming of petroleum; this process usually results in ~44% m-xylene, 20% each of o- and p-xylene, and 15% ethylbenzene
- Prior to 1940s, produced from coal tar
- Consumer products: solvents, paints or coatings, blend in gasoline (BTX)
- U.S. production of mixed xylenes in 1990: 6.2 to 12.1 billion pounds; individual isomers: p-xylene > o-xylene > m-xylene
- Odor threshold: 0.7 to 40 ppm; aromatic hydrocarbon odor
- Two primary effects of acute exposure
  - irritation
  - central nervous system toxicity (narcosis)

1

AEGL-1 Derivation

Key study:
Hastings et al., 1986.

Effects:
Subjects exposed to 0, 100, 200, or 400 ppm mixed xylene for 30 min (via olfactory hood) Mild eye irritation noted by 56, 60, 70, and 90% of the subjects, respectively. Number of eye blinks/min and respiration rate not affected

Uncertainty factors:
Interspecies UF: 1
Intraspecies UF: 3 effect was that of an irritant

Time scaling:
Irritation is threshold effect and should not vary over time; threshold value is applied to all times

AEGL-1 Values for Xylenes (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
130	130	130	130	130

2

AEGL-1

130 ppm value supported by:

- 150 ppm p-xylene for 7.5 hr - eye irritation in contact lens wearer (Hake et al., 1981)
- 230 ppm mixed xylene for 15 min - mild eye irritation and dizziness in 1/7 individuals (Carpenter et al., 1975)
- No effect levels at:

  200 ppm m- or p-xylene for 3 hr (Ogata et al., 1970)

  200 ppm m-xylene for 4 hr (Savolainen et al., 1981)

  200 ppm m-xylene for 5.5 hr (Laine et al., 1993)

3

Key Study for AEGL-2 and AEGL-3

Carpenter et al., 1975 Male albino rats: mixed xylene for 4 hr		
Conc. (ppm)	**Mortality**	**Other effects**
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate 2-3.5 hr but recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 min; all survivors prostrate but recovered promptly
9900	10/10	none stated

4

AEGL-2 and -3: Uncertainty Factors:

- Interspecies UF - 1
  - based on similar exposure effects in humans as compared with animals
  - pharmacokinetic data: interspecies UF for toxicokinetic differences < 1 using rat data to derive exposure values for humans
  - pharmacodynamic data: little difference in interspecies sensitivity: lethality data for mice and rats identical
- Intraspecies UF - 3
  - MAC for volatile anesthetics should not vary by more than factor of 2-3-fold in humans.
  - A 3-fold factor also adequate to account for moderate physical activity during exposure, resulting in greater uptake of the chemical

AEGL-2 and -3: Time Scaling

- Data inappropriate for calculation of n
- Available data indicate that concentration, not duration, is prime determinant in CNS toxicity
  - Xylene-blood conc. key in CNS toxicity
    - Readily crosses blood:brain barrier; distribution studies confirm immediate presence in CNS; elimination by 1 hr
    - Pharmacokinetic modeling in rats and humans: rapid increase in blood conc. first 15 min with minimal increases thereafter (hyperbolic curve)
    - Human data: initial rapid increase in blood conc., but then levels off
      while
    - Human and animal data indicate that increasing exposure conc. correlate with increases in venous blood conc.

AEGL-2 Derivation

Key study:
Carpenter et al., 1975.

Effects:
Poor coordination resulted when rats exposed to 1300 ppm mixed xylene for 4 hours. Represents threshold for reversible equilibrium disturbances.

Uncertainty factors:
Interspecies UF: 1
Intraspecies UF: 3

Time scaling:
Data indicate concentration, not duration, is prime determinant in xylene-induced CNS toxicity, so threshold value applied to all times

AEGL-2 Values for Xylenes (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
430	430	430	430	430

AEGL-2

430 ppm value supported by:

- Preponderance of data of 4-hr exposures in rats:
  - EC_{50} for decreased rotarod performance was 1982 ppm (Korsak et al., 1993)
  - minimum narcotic concentrations for m-, o-, and p-xylene ranged from 1940-2180 ppm (Molnar et al., 1986);
  - exposure to 1600 ppm p-xylene:
    - resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989)
    - induced flavor aversion (Bushnell and Peele, 1988),
    - caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988).
- Dogs: 1200 ppm for 4 hr represented threshold for eye irritation (Carpenter et al., 1975)

AEGL-2

430 ppm value supported by:

- Numerous human studies investigated the effects of combining peak exposures with or without exercise and found either no effect, or reported only minimal CNS effects:
  - 200 ppm m-xylene with 20 min peaks of 400 ppm (Seppalainen et al., 1989; 1991; Laine et al., 1993; Savolainen and Linnavuo, 1979)
  - 135 ppm m-xylene with 20 min peaks of 400 ppm (Savolainen et al., 1984; 1985a, b)
  - 140 ppm m-xylene with 10 min peaks of 400 ppm (Riihimaki and Savolainen, 1980; Savolainen and Riihimaki, 1981)
- Difficultly in defining AEGL-2 level for xylene comes from "all-or-nothing" continuum of toxicity: toxicity ranges from mild irritation to narcosis, with little happening in between.

AEGL-3 Derivation

Key study:
Carpenter et al., 1975.

Effects:
Prostration in all 10 rats exposed to 2800 ppm for 4 hr, with recovery occurring 1-hr post exposure; full recovery by next day. Represents threshold for narcosis; no-effect level for death

Uncertainty factors:
Interspecies UF: 1
Intraspecies UF: 3

Time scaling:
Data indicate concentration, not duration, is prime determinant in xylene-induced CNS toxicity, so threshold value applied to all times

AEGL-3 Values for Xylenes (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
930	930	930	930	930

AEGL-3

930 ppm value supported by:

- 15 min exposure to 690 ppm resulted in eye irritation and dizziness and/or lightheadedness in human volunteers (Carpenter et al., 1975)
- 30 min exposure to concentrations as high as 700 ppm xylene resulted in headache, nausea, vomiting, dizziness or vertigo, eye irritation, or nose or throat irritation (Klaucke et al., 1982)

Summary of AEGL Values for Xylenes (ppm)					
Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	130	130	130	130	130
AEGL-2	430	430	430	430	430
AEGL-3	930	930	930	930	930

XYLENES

- January meeting motions:
  - Use 130 ppm for AEGL-1 values from 10 min up to 8 hr
  - AEGL-2 values would be 430 ppm for the 1-, 4-, and -8 hr time points
  - AEGL-3 values would be 930 ppm for the 1-, 4-, and 8-hr time points
  - Based upon data suggesting that blood-xylene concentrations will equilibrate in the body for some period longer than 1 hr, proposed to perform pharmacokinetic modeling to extrapolate xylene concentrations to the 10- and 30-min exp. time points, and proposal amended to reconsider these 10- and 30-min values for AEGL-2 and AEGL-3 at the next meeting

- Dr. Ursula Gundert-Remy performed the modeling calculations for m-xylene.
- Assumptions used were:
  - one-compartment-model with continuous administration (like an infusion)
  - the plasma level for AEGL-2 (at 10 min and at 30 min, respectively) is the same as the plasma level after 4 hr administration of 430 ppm
  - the plasma level for AEGL-3 (at 10 min and at 30 min, respectively) is the same as the plasma level after 4 hr administration of 930 ppm
  - Kinetics were calculated based on the information in Table 11, page 52 in the NAC/Draft: 12/2000

Summary of Proposed AEGL Values for Xylenes [ppm (mg/m³)]

Level	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	130 (560)	130 (560)	130 (560)	130 (560)	130 (560)	Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 min (Hastings et al., 1986)
AEGL-2	1200 (5200)	570 (2500)	430 (1900)	430 (1900)	430 (1900)	Rats exposed to 1300 ppm mixed xylenes for 4 hr exhibited poor coordination (Carpenter et al., 1975)
AEGL-3	2500 (11,000)	1200 (5200)	930 (4000)	930 (4000)	930 (4000)	Rats exposed to 2800 ppm mixed xylenes for 4 hr exhibited prostration followed by a full recovery (Carpenter et al., 1975)

- 10- and 30-minute values for AEGL-2 and AEGL-3 based on the kinetic parameters for p-xylene were also calculated and are:

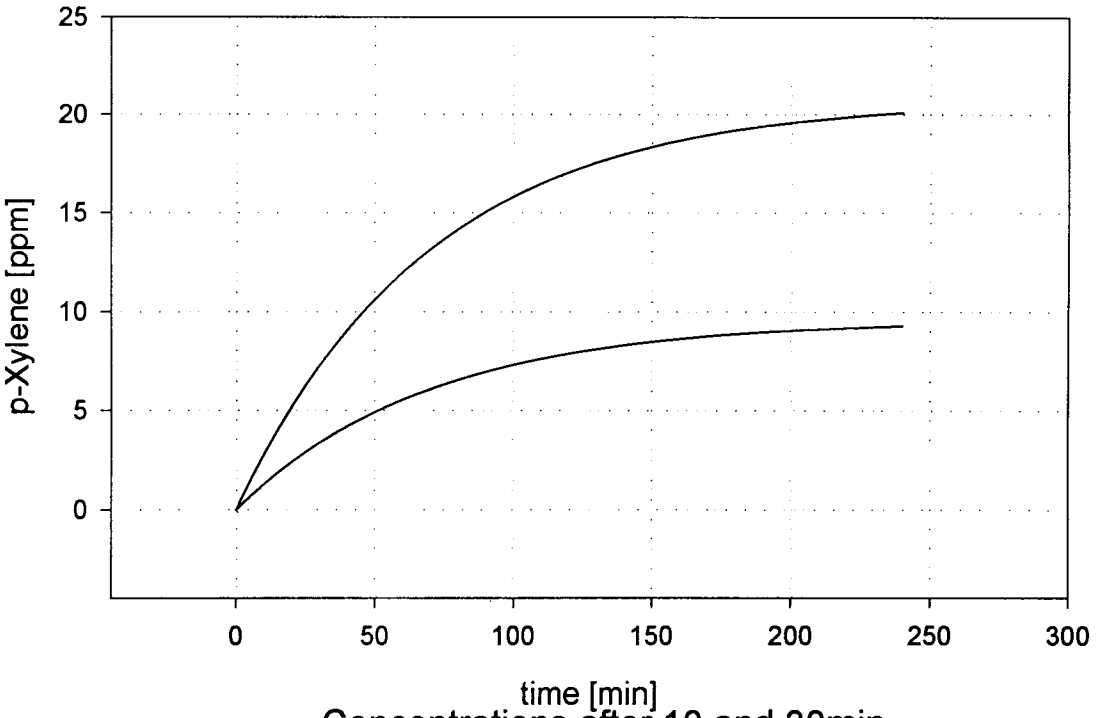
	10 minutes	30 minutes
AEGL-2	3100 ppm	1200 ppm
AEGL-3	6700 ppm	2600 ppm

It should be stated that the blood concentrations measured in the human volunteers were for m-xylene, following controlled exposures to m-xylene. Therefore, it would be more appropriate to use the 10- and 30-minute AEGL-2 and -3 levels based on the m-xylene data.

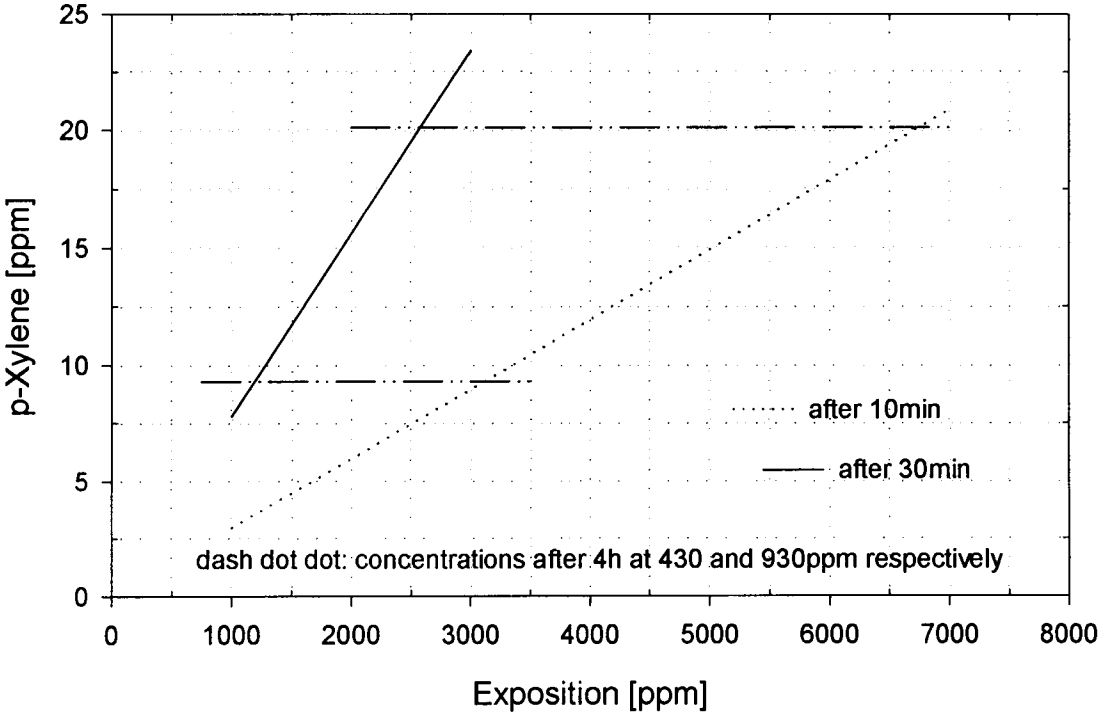
Conc. (ppm)	# of subj.	Time into exp.(h)	Venous blood xylene conc. (μmol/L)*	Comments	Reference
100*	8	1	18.4 ± 5.3	m-Xylene, odor masked with peppermint oil	Savolainen et al., 1980
		1.67	13.3 ± 2.2		
		2	21.6 ± 6.3		
		3	13.4 ± 2.9		
200*	9	0.25	16.6 ± 4.8 (μmol/L)	m-Xylene, odor masked with peppermint oil	Laine et al., 1993
		0.33	17.3 ± 5.5		
		0.67	21.3 ± 5.4		
		2	28.5 ± 5.2		
200	6	1.17	24.9 ± 2.1	m-Xylene, odor masked with peppermint oil (<1.0 ppm)	Savolainen et al., 1981
		2.5	26.7 ± 3.4		
		3.75	28.6 ± 3.5		
20	1	1	0.24 (ppm; w/w)	p-Xylene, Subjects subdivided into 3 daily groups for 1, 3, or 7.5 hour-long exposures. Males exposed to 100 ppm for the 1st week (5 d/wk), 20 ppm the 2nd wk, and 150 ppm the 3rd wk. Values reported are for first exp. day of each new week.	Hake et al., 1981
	2	3	0.41 ± 0.09		
	3	7.5	0.42 ± 0.03		
100	2	1	1.23 ± 0.18		
	2	3	1.65 ± 0.50		
	4	7.5	1.29 ± 0.21		
150	2	1	2.04 ± 0.76		
	2	3	3.18 ± 0.11		
	4	7.5	3.86 ± 0.65		

* Unless otherwise noted

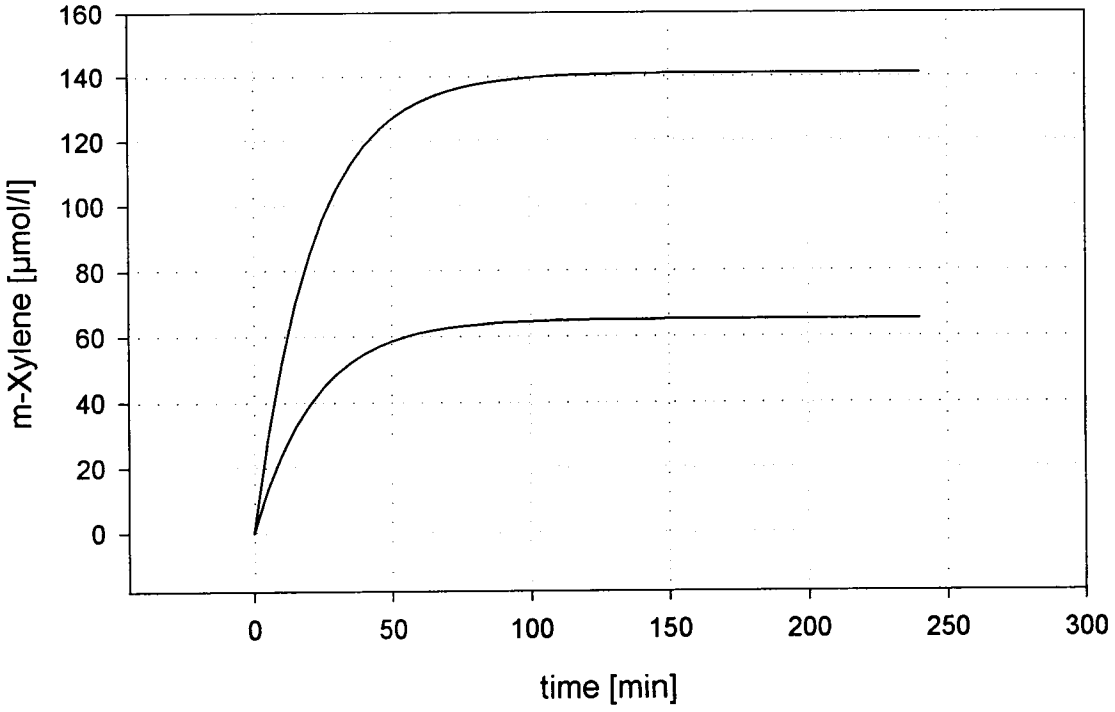
Concentration-time prediction
upper: 930ppm
lower: 430ppm



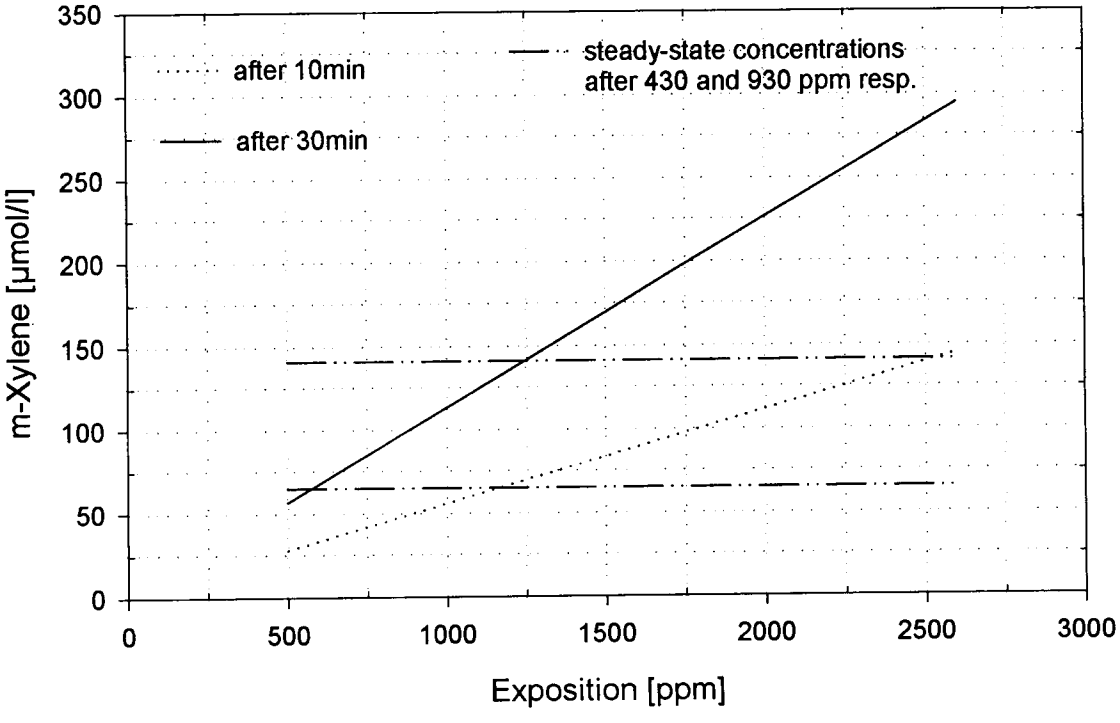
Concentrations after 10 and 30min
as a function of exposition



Concentration-time prediction
upper: 930ppm
lower: 430ppm



Concentrations after 10 and 30min
as a function of exposition



```
PROGRAM: XYLHCO.CSL
!HUMAN m-XYLENE CONVENTIONAL MODEL LIKE THE ORIGINAL ANDERSEN FILE
!CINT HAS BEEN DEFINED ACCORDING TO MGA

INITIAL

!'Section of the Program Where Values are Initialized'
!'Volumes and Weights Calculated Here:'
 CONSTANT     BW = 70          !$'Body Wt of Animals (kg)'
 CONSTANT    VFC = 0.23        !$'Fraction Body in Fat Comp.'
 CONSTANT    VSC = 0.62        !$'Fraction Body in Muscle Comp.'
 CONSTANT    VLC = 0.0314      !$'Fraction Body in Liver Comp.'
 CONSTANT    VRC = 0.0371      !$'Fract Body in Rapidly Perf.Comp.'
 CONSTANT  VBL2C = 0.059       !$'Volume Blood (L/kg)'

!'Convert Fraction Body Wts to Actual Organ/Compartment Wts:'
VF = VFC*BW
VS = VSC*BW
VL = VLC*BW
VR = VRC*BW
VBL2 = VBL2C*BW

!'Flow Rates Calculated Here:'

 CONSTANT    QPC = 15.         !$'Allometric Constant:Ventilation'
 CONSTANT    QCC = 15.         !$'Allometric Constant:Cardiac Output'
 CONSTANT    QLC = 0.24        !$'Fraction Cardiac Output to Liver'
 CONSTANT    QFC = 0.05        !$'Fraction Cardiac Output to Fat'
 CONSTANT    QRC = 0.52        !$'Fract Cardiac Output to Rich Perf'
 CONSTANT    QSC = 0.19        !$'Fract Cardiac Output to Slow Perf'

!'Calculate Total Flow Rates from Allometric Equations:'
  QP = QPC*BW**0.74            !$'Alveolar Ventilation Rate (L/hr)'
  QC = QCC*BW**0.7             !$'Cardiac Output (L/hr)'

!'Calculate Actual Blood Flow to Each Organ:'
QL = QLC*QC
QF = QFC*QC
QR = QRC*QC
QS = QSC*QC

!'Partition Coefficients for Chemical:'
 CONSTANT     PL = 3.02        !$'Liver/Blood Partition Coefficient'
 CONSTANT     PF = 77.8        !$'Fat/Blood Partition Coefficient'
 CONSTANT     PS = 3.0         !$'Muscle/Blood Partition Coefficient'
 CONSTANT     PR = 4.42        !$'Richly/Blood Partition Coefficient'
 CONSTANT     PB = 26.4        !$'Blood/Air Partition Coefficient'
```

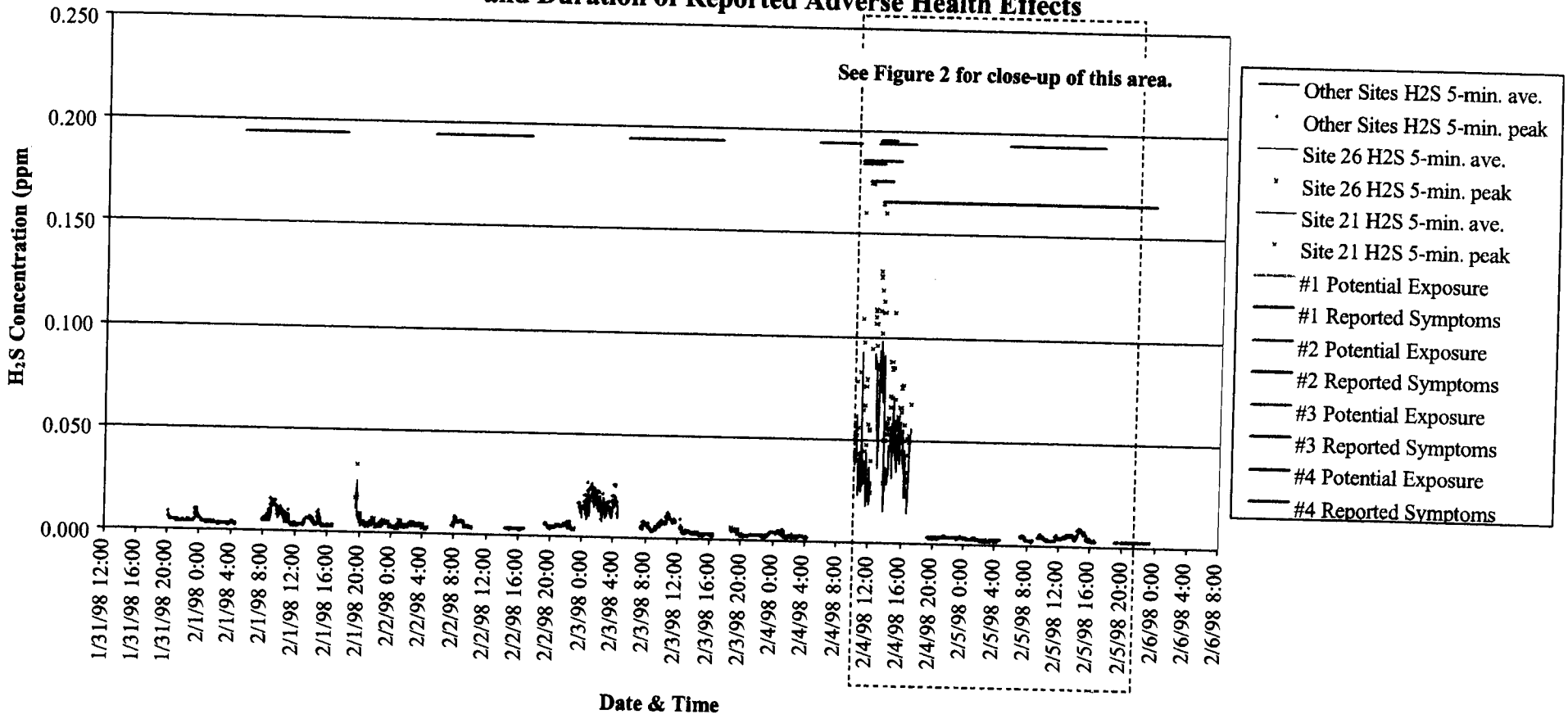
```
!'Constants related to DCM Metabolism:'
 CONSTANT  VMAXC = 8.4        !$'Allometric Const to calc VMAX'
   VMAX = VMAXC*BW**0.7       !$'Max rate of MFO metab (mg/hr)'
 CONSTANT     KM = 0.20       !$'Michaelis Constant for MFO (mg/L)'
 CONSTANT    KFC = 0.00       !$'Allometric Const to calc KF'
   KF = KFC/BW**.3            !$'1st Order Rate Const, GSH metab (hr-1)
'

!'Definition of Chemical Exposure Routes/Amounts/Times:'
 CONSTANT   CONC = 50          !$'Inhaled DCM Concentration (mg/L)'
  CONSTANT  TCHNG = 24.0       !$'Time when Inhalation of DCM stops'
 CONSTANT  TSTOP = 8.0        !$'Time when Simulation Stops'
 CONSTANT  MOLWT = 106.17

   SCHEDULE DS1 .AT. TCHNG    !$'Use DISCRETEs at Discontinuities'

END                           !$'END of INITIAL Section of Program'

DYNAMIC

   DISCRETE DS1               !$'Turn DCM inhalation On/Off'
      CIZONE = 0.0
   END $'OF DISCRETE DS1'

ALGORITHM       IALG=2
NSTEPS          NSTP=1000
MAXTERVAL       MAXT=1.0E+10
MINTERVAL       MINT=1.0E-10
CINTERVAL       CINT=0.01

DERIVATIVE
        R       =(VMAX/KM)+(KF*VL)
        C       =1/PB
        EL      =((R*QL)/(R+QL))/QL

        CASS    =CI/(C+(QLC*EL))

        CVSS    =CASS*(1-QLC*EL)
        CSSS    =PS*CASS
        CRSS    =PR*CASS
        CFSS    =PF*CASS
        CLSS    =PL*CASS*(1-EL)

        CVLSS   =CASS*(1-EL)
        CVFSS   =CASS
        CVRSS   =CASS
        CVSSS   =CASS
```

```
      PER     =((CA-CASS)/CA)*100

      FSAA    =CA/CASS
      FSSV    =CV/CVSS
      FSSL    =CL/CLSS
      FSSS    =CS/CSSS
      FSSR    =CR/CRSS
      FSSF    =CF/CFSS
      FSSF2   =1-EXP(-RCF*T)

      RCF     =QF/(PF*VF)                    !RATE CONSTANT (hr-1)
      RCL     =(QL+(VMAX/KM))/(PL*VL)
      RCR     =QR/(PR*VR)
      RCS     =QS/(PS*VS)

      TCF     =1/RCF                         !TIME CONSTANT (hr)
      TCL     =1/RCL
      TCR     =1/RCR
      TCS     =1/RCS

      TSS     =7*TCF                         !TIME TO STEADY STATE

!'CI = Concentration of DCM in inhaled air (mg DCM/L)'
   CIZONE = RSW( T .GE. TCHNG, 0.0, 1.0)
       CI = CONC*CIZONE*MOLWT/24450.0              !$'Convert to mg/
L'

!'CA = Arterial blood concentration (mg DCM/L)'
       CA = (QP*CI+QC*CV)/(QP/PB+QC)
       CX = CA/PB
    CXPPM = CX*24450/MOLWT
      CEX = .7*CX                          !$'Conc DCM in exhaled air'

     CEX1 = CEX+.3*CI
     AUCB = INTEG(CA,0.0 )

!'AX = Amount of DCM exhaled (mg)'
      RAX = QP*CX
       AX = INTEG(RAX, 0.0 )

!'AF = Amount of DCM in fat compartment (mg)'
      RAF = QF*(CA -CVF)
       AF = INTEG(RAF, 0.0 )
      CVF = AF/(VF*PF)
       CF = AF/VF

!'AL = Amount of DCM in liver compartment (mg)'
      RAL = QL*(CA - CVL) - RAMT
```

```
      AL = INTEG(RAL, 0.0 )
     CVL = AL/(VL*PL)
      CL = AL/VL
   AUCCL = INTEG(CL,0.0)

!'AS = Amount of DCM in slowly perfused tissues (mg)'
     RAS = QS*(CA - CVS)
      AS = INTEG(RAS, 0.0 )
     CVS = AS/(VS*PS)
      CS = AS/VS

!'AR = Amount of DCM in rapidly perfused tissues (mg)'
     RAR = QR*(CA -CVR)
      AR = INTEG(RAR, 0.0 )
     CVR = AR/(VR*PR)
      CR = AR/VR

!'AM1 = Amount of DCM metabolized by Satur Pathway (MFO) in mg'
    RAM1 = (VMAX*CVL)/(KM + CVL)
     AM1 = INTEG(RAM1, 0.0 )
    CAM1 = AM1/VL
   AUCM1 = INTEG(CAM1,0.0)

!'AM2 = Amount of DCM metabolized by 1st Order Path (GSH) in mg'
    RAM2 = KF*CVL*VL
     AM2 = INTEG(RAM2, 0.0 )
    CAM2 = AM2/VL
   AUCM2 = INTEG(CAM2,0.0)

!'Total rate/amount of metabolism (MFO + GSH)'
    RAMT = RAM1+RAM2
     AMT = AM1+AM2
    CAMT = CAM1+CAM2
   AUCMT = INTEG(CAMT,0.0)

!'CV = Algebraic Solution for Venous Blood DCM Conc (mg/L)'
      CV = (QF*CVF + QL*CVL + QS*CVS + QR*CVR)/QC
   AUCCV = INTEG(CV,0.0)


!'AI = TOTAL MASS INPUT (MG)'
     RAI = QP*CI
      AI = INTEG(RAI, 0.0 )
   DOSEI = AI/BW

!'TMASS = Mass Balance (mg)'
   TMASS = AF + AL + AS + AR + AMT + AX
```

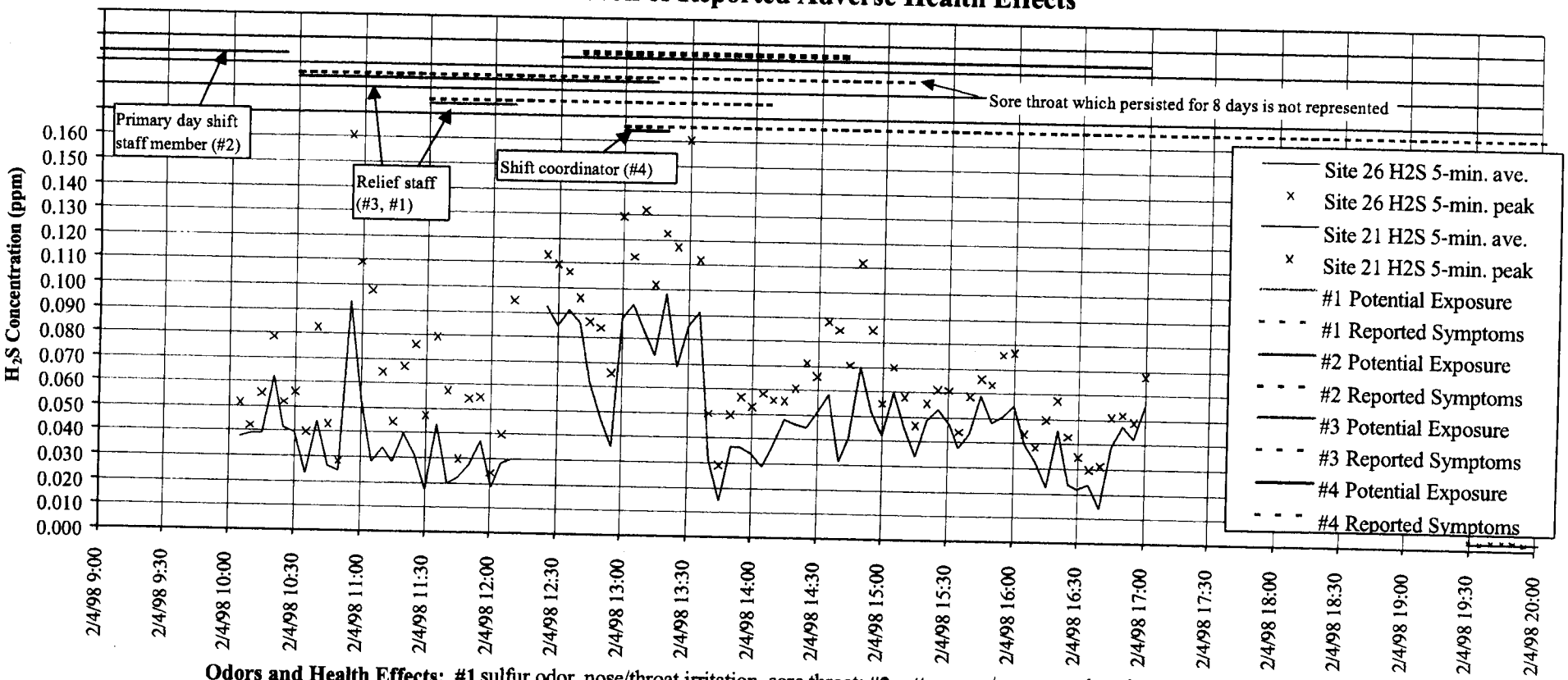
```
!'DOSE = Net amount absorbed (mg)'
     DOSE = AI - AX
    DOSE2 = DOSE/BW

TERMT(T.GE.TSTOP)                !$'** Termination Condition for Model *
*'

END                              !$'End of DERIVATIVE'
END                              !$'End of DYNAMIC'
END                              !$'End of PROGRAM'
```

Figure 1. Van 753 Monitored H_2S Concentrations, Potential Exposure Duration (staff presence), and Duration of Reported Adverse Health Effects



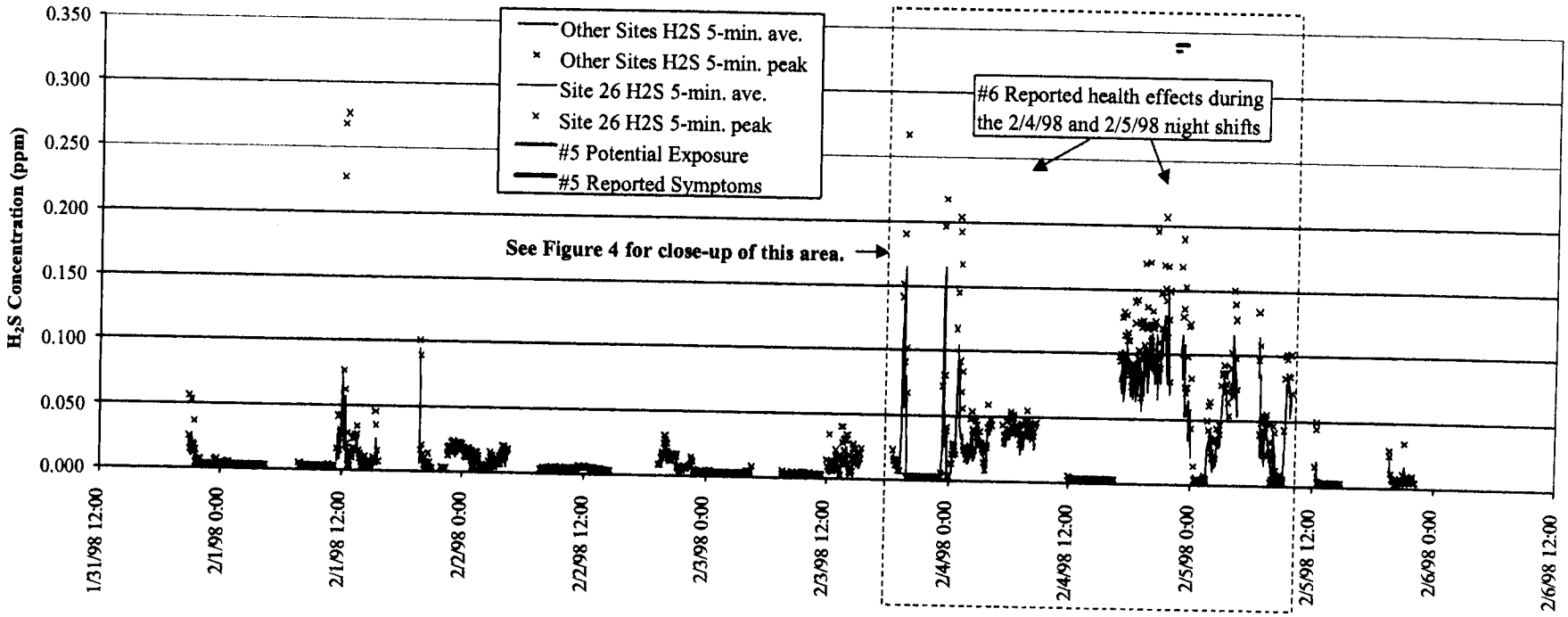
Attachment 10

Figure 2. Van 753 Monitored H_2S Concentrations, Potential Exposure Duration (staff presence), and Duration of Reported Adverse Health Effects



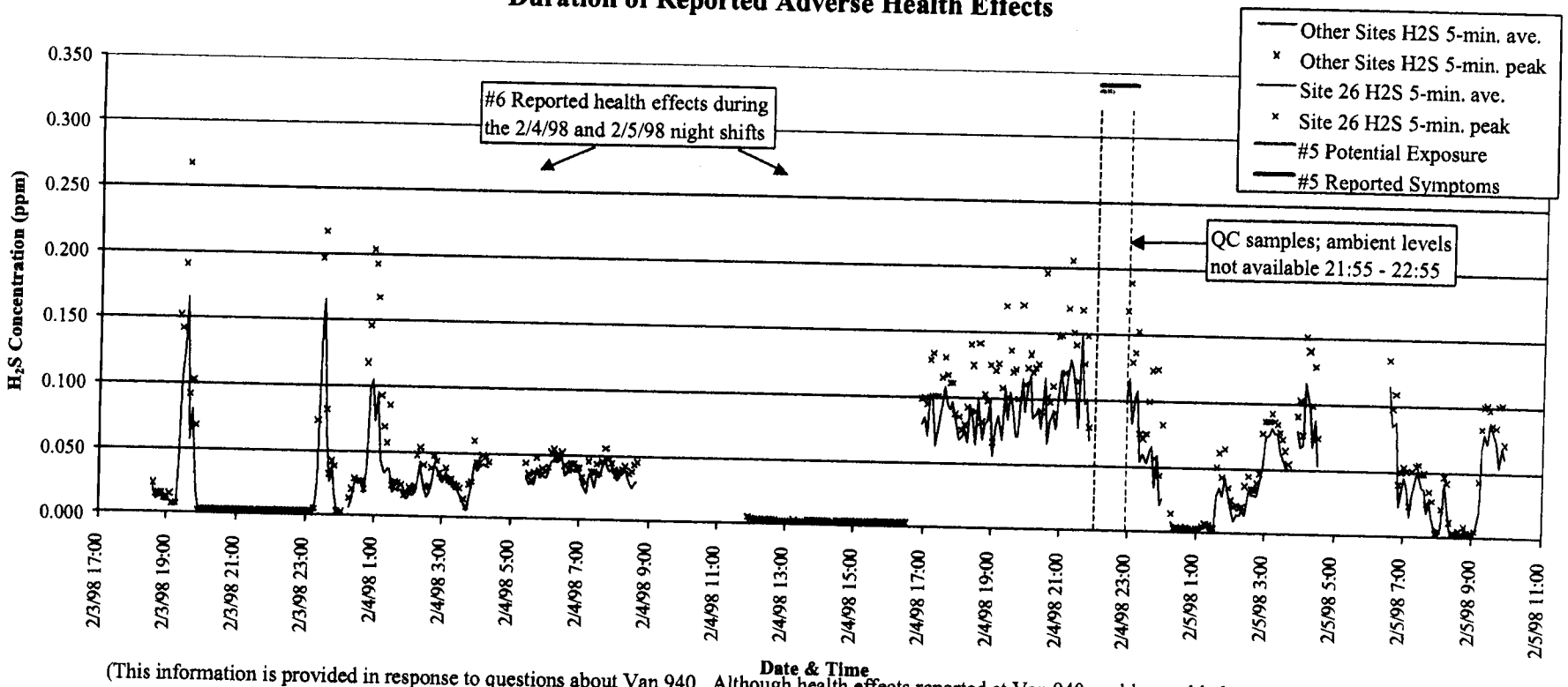
Odors and Health Effects: **#1** sulfur odor, nose/throat irritation, sore throat; **#2** rotten eggs/sour gas odors, headache, sore throat; **#3** sulfur odor, headache, sore throat; **#4** sulfur/rotten egg odors, exacerbated pre-existing scratchy throat to hoarseness though 2/5/98.

Figure 3. Van 940 Monitored H_2S Concentrations, Potential Exposure Duration (staff presence), and Duration of Reported Adverse Health Effects



(This information is provided in response to questions about Van 940. Although health effects reported at Van 940 could arguably be associated with H2S, these personnel could have been concomitantly exposed to carbon monoxide. Therefore emphasis is placed on health effects reported at Van 753.)

Figure 4. Van 940 Monitored H_2S Concentrations, Potential Exposure Duration (staff presence), and Duration of Reported Adverse Health Effects



(This information is provided in response to questions about Van 940. Although health effects reported at Van 940 could arguably be associated with H2S, these personnel could have been concomitantly exposed to carbon monoxide. Therefore emphasis is placed on health effects reported at Van 753.)

TNRCC Response to Questions Posed by AEGL Committee Members on the Report by Laboratory and Mobile Monitoring Section of the Texas Natural Resource Conservation Commission Entitled, "Corpus Christi Mobile Laboratory Trip, January 31 - February 6, 1998; Real-Time Gas Chromatography and Composite Sampling, Sulfur Dioxide, Hydrogen Sulfide, and Impinger Sampling".

General Comment

Mobile Monitoring staff of the Texas Natural Resource Conservation Commission reported adverse health effects consistent with H_2S exposure during time periods when measured ambient 5-minute average H_2S concentrations ranged from 0.015 to 0.098 ppm (average 0.059 ppm). The corresponding peak concentrations during those 5-minute periods ranged from 0.024 to 0.161 ppm. (Based on Van 753 data.)

Hydrogen sulfide monitoring data (5-minute average and peak concentrations) is presented in Figures 1 and 2 (Van 753) and Figures 3 and 4 (Van 940). Superimposed on that monitoring data are the periods of potential exposure and reported health effects of the monitoring staff. Van 940 information is presented in response to several questions. However, it should be noted (as previously reported on the poster presentation), that the two Van 940 individuals who reported H_2S-related effects may have been concomitantly exposed to carbon monoxide. Therefore, emphasis is placed on the four individuals exposed at Van 753. Reported odors and health effects are summarized below.

Van	Individual	Odor Quality	Odor Intensity (Scale 1 - 5)	Health Effects
Van 753	Case 1	sulfur	3	nose/throat irritation, sore throat
	Case 2	rotten egg, sour gas	4	headache, sore throat
	Case 3	sulfur	3	headache, sore throat, nausea
	Case 4	sulfur, rotten eggs	3	exacerbated pre-existing scratchy throat to hoarseness
Van 940	Case 5	H_2S	3 or 2.5	Sore throat, nose/throat irritation, nausea
	Case 6	rotten eggs, sour	3	headache, chest tightness, irritability

It is important to note that the primary purpose of mobile monitoring projects is to measure concentrations of air pollutants in the vicinity of specified facilities. Although it was not the primary goal to perform a rigorous concomitant epidemiological study of associated health effects during the January 31 - February 6, 1998 mobile monitoring trip, a secondary duty of the monitoring staff is to note any adverse health effects experienced during the course of their regular duties. Staff documented health effects on Monitoring Operations Hazard Identification Forms at the time of occurrence or as soon as performance of monitoring duties would allow. In addition, a staff epidemiologist interviewed and administered a questionnaire to the monitoring staff within two to three weeks after their return from the monitoring trip.

One should also note that the ambient monitoring experience of the staff members ranged from 3 to 8 years; mean years of experience was 4.6 years. Staff have experienced many odors and indirect and direct health effects in the course of their experience, and do not lightly report such effects. Rather, when they report effects, it is because the effects are especially notable/intense, are clearly associated ambient air pollutants, and stand out above what they routinely experience. Therefore, the effect levels reported by these staff are likely not Lowest Observed Adverse Effect Levels.

Finally, these data are unique in Texas air monitoring experience in that they represent a relatively "pure" exposure to low levels of H_2S. Although staff have previously reported adverse effects associated with levels of H_2S measured on previous trips, corresponding levels were 2 to 4 ppm. Further, on past monitoring trips, monitoring personnel reported difficulty in determining whether adverse effects and/or odors experienced were associated specifically with H_2S. It could not be ruled out that effects were, instead, caused by exposure to sulfur dioxide (SO_2) and reduced sulfur compounds, such as mercaptans. It is interesting to note that concurrent exposure to other sulfur compounds and VOCs was negligible during the periods that H_2S-related health effects were reported on this trip. Specifically, although the highest five-minute SO_2 concentration reported during this particular monitoring trip was 0.200 ppm (peak 0.242 ppm), the five-minute SO_2 concentrations ranged from only 0.002 to 0.039 ppm during periods when adverse health effects were reported.

Responses to Specific Questions

The questions/comments are followed by **TNRCC responses in bold.**
The questions were posed by 4 individuals. Each set of questions is identified as individual 1, 2, 3, and 4.

Individual 1

1. In addition to the real-time gas chromatograph samples for H_2S, the (mobile monitoring trip) report states (page 1, paragraph 2) that 4 impinger samples for H_2S were also taken. When, where, and for how long were these samples taken during the sampling period January 31-

February 6, 1998? How do the results compare with those for the real-time samples for H_2S reported in the Tables 23-25?

H_2S was measured real-time (continuous emission monitor, CEM) using a Dasibi 4109 H_2S-to-SO_2 converter in conjunction with a Monitor Labs 9850 SO_2 analyzer. In addition to this CEM monitoring, four 30-minute composite impinger samples were collected. The following table describes the impinger samples and shows the corresponding CEM 30-minute average concentrations measured at the same sites that the impinger samples were collected:

Impinger 30-minute Samples					CEM 30-min. Average
Sample	**Date/Time**	**Location**	**Duration**	**ppm**	**ppm**
CI 01	2/3/98 1945 - 2015	Site 26	30 min.	< 0 .040 *	0.004
CI 01 Comment: After the wind direction changed from NNW to ENE, high H_2S levels (0.057-0.165 ppm 5-min. ave., 0.267 ppm peak) were measured from 19:20 to 19:45. This 30-min. impinger sample was initiated at 19:45, but the wind direction changed again, and ambient levels decreased to below detection limits for both the impinger and CEM methods.					
CI 02	2/4/98 1104 - 1135	Site 26	31 min.	0.040	0.032
CI 03	2/4/98 0055 - 0125	Site 26	30 min.	< 0 .040 *	0.053
CI 16	2/4/98 1300 - 1330	Site 26	30 min.	0.058	0.083
CI 16 duplicate	2/4/98 1300 - 1330	Site 26	30 min.	0.069	

* not detected, method detection limit = 0.040 ppm

2. Page 3, paragraph 1 - To what mobile laboratory (van?) does this QC failure apply? Is there a difference between a mobile laboratory and a Van? If so, please describe the differences.

The following five sampling vehicles were deployed:

Mobile Laboratory	**monitored selected VOCs, H_2S, and SO_2**
Van 753	**monitored H_2S and SO_2**
Van 940	**monitored H_2S and SO_2**
Van 219	**monitored selected VOCs**
Van 754	**monitored selected VOCs**

The mobile laboratory is a 42-foot trailer pulled by a truck, while the Vans are motorized vehicles. The mobile laboratory is larger than a Van and carries more equipment than a

Van. After being pulled to the monitoring area, the mobile laboratory is parked in one location for the duration of the monitoring event, while the vans are relocated as needed. The Quality Control (QC) Summary of the mobile monitoring report referenced by the commenter and attached for reference lists the QC failures and specifies the affected chemical(s), quantifies the potential measurement bias, and specifies the applicable Van or the mobile laboratory.

3. Page 4, paragraphs 1, 2, 3 and 4. Where were the individuals located during the sampling periods and in relation to the intake for the sampling devices? At what elevation relative to the ground were the samplers located?

Sampling staff who reported health effects were inside and/or immediately outside the specified Vans. Van doors were open and monitoring staff report mixing of air inside and outside of open Vans due to wind.

Relative Heights from the Ground (inches)

Impinger Sampler Inlet	44
Breathing Height	70 to 108 (approximate, assuming 5'10" personnel and depending on location inside/outside of Van)
Van 753 Sampler Inlet	132
Van 940 Sampler Inlet	146

4. The devices used to determine H_2S concentrations apparently were real-time area samplers. How was the H_2S concentration established in the breathing zone of each individual?

Monitoring technology is not available for sampling personal H_2S exposure at the reported levels. Nevertheless, we believe the measured ambient concentrations reasonably represent exposure concentrations. When monitoring staff experienced adverse health effects, they and their sampling vans were located in an H_2S plume downwind of a sour water tank and sulfur recovery units at a refinery. It is the staff's duty to attend their instruments and record maximum concentrations (i.e., stay in the plume). Their ability to stay in the plume is demonstrated by the measured concentrations, and staff were either inside or immediately outside the open vans. Breathing heights were within the range of sampler inlet heights.

5. For the individuals who reported symptoms of health effects, what was the time of onset of these symptoms relative to their arrival at the respective sampling sites?

See table below and, also, Figures 1 and 2.

Individual	Time of Arrival at Site	Symptoms Started	Time of Departure from Site	Symptoms Ended
Case 1[b] Van 753	~ 11:30 2/4/98	11:30 2/4/98	12:10 2/4/98	14:10 2/4/98
Case 2[a] Van 753	12:30 2/4/98 return from break	12:40 2/4/98	~ 17:00 2/4/98	14:45 2/4/98
Case 3[b] Van 753	10:30 2/4/98	10:30 2/4/98	13:15 2/4/98	15:15 2/4/98 (headache) 2/12/98 (sore throat)
Case 4[b] Van 753	~13:00 2/4/98	13:00 2/4/98	13:20 2/4/98	2/5/98 (hoarseness)
Case 5 Van 940[c]	~ 22:00 2/4/98	22:00 2/4/98	22:20 2/4/98	23:05 2/4/98
Case 6 Van 940[c]	~ 17:00 2/3/98 ~ 16:55 2/4/98	19:15 2/3/98 ~ 16:55 2/4/98	~ 05:00 2/4/98 ~ 05:00 2/5/98	~ 05:15 2/4/98 ~22:00 2/4/98

[a] Case 2 was primary day shift staff.

[b] Cases 1, 3 and 4 were relief staff or shift coordinator.

[c] Van 940 staff's symptoms were not previously reported because of possible concomitant exposure to carbon monoxide, but are presented here in support of Individual 2 Question Number 1.

6. Where were these individuals located when they first reported symptoms indicating adverse health effects?

Sampling staff were inside or immediately outside (within 10 feet) of the specified Vans.

7. What was the relative humidity during the sampling periods?

Relative humidity, which was monitored only at the mobile laboratory, was 60% to 70%. The mobile laboratory was located 1 mile south-southeast of Sites 21 and 26 where the adverse health effects were reported.

8. Do any of the vans have a generator to power the operation of the equipment or are all devices battery powered? If a generator, where is it located and what type of fuel does it use? At what elevation is the exhaust released from this engine? What is the horsepower of the engine? What is its fuel consumption per hour? Does this engine have an operating catalytic converter? Were measurements for exhaust chemicals made during any of the sampling periods, e.g. oxides of nitrogen, carbon monoxide or other exhaust fumes which may be relevant to throat irritation and headache?

Each H_2S/SO_2 van (753 and 940) had one propane-powered generator to power the equipment. In Van 753, the generator was located under the rear of the vehicle. The generator in Van 940 was mounted in a plywood box inside the van with access from the outside of the van. Elevation of exhaust release may be found in the table below. Propane-powered generators are rated only in watts (not horsepower) as specified in the table below and do not have catalytic converters. Carbon monoxide levels were monitored inside the Vans with Nighthawk CO alarms with digital displays. During air monitoring, vans are parked in an orientation such that the generator is exhausted downwind of the sampling inlet.

Van	Generator Exhaust Height from Ground	Generator Wattage Rating	Approx. Propane Consumption
753 H_2S/SO_2	22 inches (horizontal)	6500 watts	1.1 gal/hour
940 H_2S/SO_2	approx. 16 inches (straight down)	6300 watts	0.9 gal/hour

As previously reported in a poster presentation, the health effects experienced by Van 940 workers while they were in the H_2S plume were not presented in the poster because of possible concomitant exposure to elevated CO levels. This was caused by a generator exhaust leak into Van 940 which has since been decommissioned. It should be noted that Van 940 staff spent most of their time outside the van because of the CO problem. The newer-designed Van 753 did not have these problems.

9. The poster presentation of the report addresses the exposure of individuals for 30 minutes. Yet the actual time of exposure to H_2S is longer in several instances. For example, in Table 24 of the full report individuals were on sampling site 26 of sampling period 7 from 18:30 on 2/3/98 until 04:20 on 2/4/98. Why isn't the period of H_2S exposure in this case reported as 9 hours and 50 minutes? Please explain, in all instances in which exposures are longer than 30 minutes, why the longer time periods of exposure weren't referenced?

The poster presented health effects in four individuals who variably reported the time of occurrence between 10:30 and 13:30 on 2/4/98 outside Van 753 at Sites 21 and 26 (see Health Effects Reports section of poster). The highest 30-minute average H_2S measured at Van 753 during these 3 hours was 0.084 ppm with a 0.161 ppm peak concentration. The highest 30-min. average was presented in the context of the Texas regulatory standards for H_2S which are based on a 30-minute averaging time. The 3-hour (10:30 - 13:30) average was 0.051 ppm.

In the example given in the question, the time period of H_2S exposure would not be reported as 9 hours and 50 minutes because measured H_2S levels were less than the method detection limit (<0.003 ppm) for 3 hours and 20 minutes of that time period (18:30 2/3/98 to 04:20 2/4/98, Site 26, Van 940, Table 24). In addition, the poster did not present any adverse health effects experienced at Van 940 because of possible concomitant exposure to carbon monoxide. Please also refer to Figures 1 and 2.

10. Table 18. The date reported for site 26 is 2/4/97. Is this a typographical error or is it correct?
Table 19. The date reported for sites 26 and 32 is 2/4/97. Is this a typographical error or is it correct?
Table 20. The date reported for site 26 and 32 is 2/4/97. Is this a typographical error or is it correct?

These are typographical errors; the year was 1998. Other typographical errors include:
Table 19 title, year should be 1998 instead of 1996; and,
Table 21 dates for sites 32 and 26, year should be 1998 instead of 1997.

11. All the samples were area samples. They obtained none with personal samplers. Is there any data that reflect H_2S concentrations as measured by personal samplers?

No. Personal sampling devices that are capable of detecting and recording H_2S at the reported exposure levels are not available. While personal sampling data is not available, we believe the measured ambient concentrations reasonably represent exposure concentrations. When monitoring staff experienced adverse health effects, they and their sampling vans were located in an H_2S plume downwind of a sour water tank and sulfur recovery units at a refinery. It is the staff's duty to attend their instruments and record maximum concentrations (i.e., stay in the plume). Their ability to stay in the plume is demonstrated by the measured concentrations, and staff were either inside or immediately outside the open vans. Breathing heights were within the range of sampler inlet heights.

12. The report provides no indication of either thought or planning directed toward obtaining human health effects information. The human health-effects information provided is at best anecdotal and is possibly recall in nature. Was a procedure in place for collection of health effects data and was it recorded at the time of occurrence?

Yes, a procedure was in place to collect health effects information in the field. Staff documented health effects on Monitoring Operations Hazard Identification Forms at the time of occurrence or as soon as performance of monitoring duties would allow. In addition, a staff epidemiologist interviewed and administered a questionnaire to the monitoring staff (see next question).

It is important to note that the primary purpose of mobile monitoring projects is to measure concentrations of air pollutants in the vicinity of specified facilities. Although it was not the primary goal to perform a rigorous concomitant epidemiological study of associated health effects during the January 31 - February 6, 1998 mobile monitoring trip, a secondary duty of the monitoring staff is to document any adverse health effects experienced during the course of their regular duties.

13. No questionnaire was administered to obtain statistically useful or personal information from the exposed individuals. The authors provide no information about the gender, age, smoking history, general health, current medications, frequency of headache and sore throat on a typical work day of the individuals reporting health effects. Was this information collected and recorded?

Yes, in addition to the Hazard Identification Forms completed in the field, a staff epidemiologist interviewed and administered a questionnaire to the monitoring staff between February 19 and 30, 1998 (2 - 3 weeks after their return from the monitoring trip). The questionnaire collected information in the following categories: identification; demographic/personal information; smoking history/tobacco history; medication/medical history; occupational history; exposure assessment; symptoms; subjective. Concerning the specific topics listed by the commenter, the questionnaire gathered information on gender, age, smoking history, general health, and current medications, but not "frequency of headache and sore throat on a typical work day".

The six individuals who reported H_2S-related health effects ranged in age from 32 to 50 years; median age was 36 years. Two staff members were female, and four were male. The racial/ethnic distribution for all cases was white. The ambient monitoring experience of the staff members ranged from three to eight years; mean years of experience was 4.6 years. All six cases characterized the odor as either H_2S, rotten egg smell, or sulfur. Five of the six cases reported moderate odor intensity. One individual, who was the only smoker, reported the odor with a greater degree of intensity (4 on a rating scale of 1 to 5). At the time of the incident, two were taking medication (one in Van 940 was taking medication for allergies and was one of the two individuals excluded from the poster presentations due to possible concomitant carbon monoxide exposure; the second was on prescription eye drops for glaucoma). Three rated their overall health excellent; three rated their overall health good.

Individual 2

1. There were 10 individuals on the monitoring trip. Six of 10 reported health effects, but effects were reported for only 4 in the abstract and poster. What were the effects of the other 2 individuals?

Actually a total of 16 staff members were present on the monitoring trip. The poster should have noted that 10 of the 16 individuals were potentially exposed to the H_2S plume based on their assigned duties. Six of these 10 reported adverse health effects. The remaining four consisted of two individuals who traveled in-and-out of the area (one of whom was mostly upwind of the H_2S source), one individual with limited olfactory ability who was mostly upwind of the source, and one individual who reported nausea associated with odors of burning motor oil and propane. Of the six individuals who did report health effects associated with H_2S, two were not presented on the poster because of possible confounding exposure to carbon monoxide. Health effects reported by those two were as follows: (1) moderate odor, nose/throat irritation, raw throat, and slight nausea; and, (2) odor (slight, moderate and intense), headache (moderate and intense), and chest tightness.

2. There are instances in which the [H_2S] is in a range where effects could be expected, e.g.

- Van # 940, 2/1/98, 12:20, site 26, [H_2S] – 5 minute avg. – 57 ppb, peak value – 276 ppb
- Van # 940, 2/1/98, 19:40, site 26, [H_2S] – 5 minute avg. – 95 ppb, peak value – 101 ppb
- Van # 940, 2/3/98, 19:20-19:45 site 26, [H_2S] – 5 minute avg. – 38-165 ppb, peak value – 103-267 ppb
- Van # 940, 2/4/98, 16:55-21:50, site 26, [H_2S] – 5 minute avg. – 63-149 ppb, peak value – 67-207 ppb

Why weren't health effects noted and/or reported from the above monitoring events?

The poster did not present the adverse health effects experienced in Van 940 because of possible concomitant exposure to carbon monoxide. Again, odor and effects reported by monitoring personnel in Van 940 included: (1) moderate odor, nose/throat irritation, raw throat, and slight nausea; and, (2) odor (slight, moderate and intense), headache (moderate and intense), and chest tightness.

3. In the instance of the 4 individuals in which health effects were reported, these individuals were on 2 separate sampling sites (26 from 10:05-12:10; 21 from 12:25-17:00). For example, individual (case 2) reported effects only after returning from lunch, yet presumably the individual was present for the morning sampling at site 26. The H_2S concentration at site 26 in the morning and site 21 in the afternoon were comparable (site 26, 5 minute averages between 17-93 ppb; site 21, 5 minute averages 14-92 ppb). If that individual experienced effects in the afternoon, then effects should also have been experienced in the morning. Please provide an explanation of why health effects were not reported in the morning.

The H_2S levels measured during the first hour after Case 2's return from break were higher than the H_2S levels measured while Case 2 was present before the break (see table below, and also, Figures 1 and 2). This likely explains why health effects were reported after the break but not before.

Comparison of H_2S Levels (ppm) measured before and after Case 2's lunch break.

		BEFORE Break (no health effects reported)	AFTER Break (health effects reported)
Statistics for 5-min. AVERAGE data	Maximum	0.062	**0.098**
	Average	0.044	**0.076**
	Minimum	**0.038**	0.036
Statistics for 5-min. PEAK data	Maximum	0.078	**0.161**
	Average	0.056	**0.109**
	Minimum	0.042	**0.065**

4. Of the 4 individuals reported to have experienced health effects, 2 reported no odor and 2 did report odor. Yet the 2 individuals who reported health effects with no odor should have also detected an odor of H_2S because the concentrations were well above the odor threshold and odor recognition occurs at concentrations far below the odor threshold. Please provide an explanation for this apparent inconsistency.

Even though two individuals did not record odor on their Hazard Identification Forms (HIFs) in the field, but rather, completed only the health effects portion of the form, neglecting to report odor is not equivalent to reporting no odor. Upon review of the HIFs completed in the field and the questionnaires completed after returning from the monitoring trip, it was determined that all four individuals reported that they smelled sulfur, rotten eggs, and/or sour gas. The poster presentation to which the commenter is referring represented only the HIFs.

5. One individual (case 4) had a pre-existing scratchy throat. It is possible to distinguish H_2S effects from the pre-existing throat condition?

Case 4 reported that exposure to H_2S *exacerbated* the pre-existing scratchy throat condition and caused hoarseness. It is possible to distinguish between different magnitudes of a sore throat and to note the onset of hoarseness (in this case, during exposure to H_2S).

Individual 3

1. Were particulates measured during the TNRCC sampling events? This is significant because particulate materials combined with sulfur dioxide can produce a greater effect than a similar concentration of sulfur dioxide alone.

Particulate sampling was not conducted. Monitoring staff reported that particulate matter was not present at visible concentrations. During periods when adverse health effects were reported, five-minute SO_2 concentrations ranged from 0.002 to 0.039 ppm with a median level of 0.005 ppm. Given this information, we do not believe the reported health effects were caused by additive or synergistic effects of particulate and sulfur dioxide.

2. Was the sampling conducted during a flare incident at the refinery? This is significant because during such an incident particulate material is easily produced.

No flaring was observed or reported to have occurred at the refinery being monitored when health effects were reported.

According to upset/maintenance records, a different refinery approximately 3.25 miles away released 2,125 pounds of SO_2 (2/1-3/98) with flaring, and 278 pounds of nitrogen dioxide and 10 pounds nitrogen monoxide (2/4-5/98). Monitoring at this facility showed a maximum 5-minute average SO_2 concentration of 0.200 ppm on 2/2/98. The highest measured SO_2 level is well below levels that would be expected to cause adverse health effects, and no health effects were reported at any time while monitoring at this facility. These upset emissions would not be expected to contribute to the reported health effects. The location of the reported health effects was approximately 3.25 miles distant and not downwind of the upset emission source.

3. The time of onset of the health effects to the TNRCC monitoring personnel relative to the specific time point during the monitoring events was not given. Are these data available and if so, please state when each specific health effect was initially noted relative to the time point during each monitoring event in which health effects were experienced?

Please see response to Individual 1, Question Number 5.

Individual 4

1. What were the health effects/complaints reported at different measured ambient H_2S concentrations? Can the authors provide an analysis of the data that would show a dose-response relationship for the reported health effects/complaints? For example, Table 14 shows high H_2S readings for Van 940 on 2/1/98 at Site 26 (highest concentration 0.276 ppm, 30-minute average 0.118 ppm), and on 2/5/98 at Site 19 (highest concentration 0.151 ppm, 30-minute average 0.084 ppm). Were there complaints from the workers in this van during these high readings?

A variety of steady levels of H_2S was not measured. Rather, levels were either below 0.020 ppm or varying between approximately 0.03 and 0.1 ppm (when health effects were reported). Thus, a dose-response study of these data is not possible. Also, see Figures 1 and 2.

During the high H_2S measurements referenced in the question (Van 940, 11:55 - 12:20, 2/1/98, Site 26, 0.276 ppm peak), health effects were not recorded. This is not surprising since elevated levels were associated with a short-lived (less than 30 minutes) shift in wind direction; five-minute average levels ranged from 0.017 to 0.077 ppm. The 30-minute average of 0.118 ppm cited in the question actually occurred on 2/4/98 (as stated in footnote of Table 14) from 21:05 - 21:35. This 30-minute average was measured during a period of at least 5 hours during which the 5-minute average levels ranged from 0.056 to 0.149 ppm (average 0.091 ppm). The staff member responsible for working this night shift documented odor, eye irritation, and headache due to exposure to H_2S on the nights of 2/4/98 and 2/5/98. These health effects were not reported on the poster presentation due to possible concomitant exposure to carbon monoxide.

2. What was the highest concentration of H_2S at which no health effects/complaints were noted from individuals at the monitoring sites?

Approximately 0.025 ppm (5-minute average) and 0.033 ppm (instantaneous peak). Also, see response to previous question and Figures 1 and 2. This dataset does not allow a precise determination of a highest no-effect level (due to real-world conditions such as variable exposure levels). However, this data shows that adverse health effects are associated with concentrations below 0.098 ppm (5-min. ave) and 0.161 ppm (instantaneous peak) for Van 753. For informational purposes, although possible concurrent exposure to carbon monoxide occurred in Van 940, health effects were reported at H_2S levels at and below 0.165 ppm (5-min. ave.) and 0.276 ppm (instantaneous peak).

The 5-minute average H_2S concentrations monitored during exposure and effects for Van 753 staff who reported health effects ranged from 0.015 to 0.098 ppm (average 0.059 ppm). The corresponding peak concentrations during those 5-minute periods ranged from 0.024 to 0.161 ppm.

Attachment 11

HYDROGEN SULFIDE AEGL-1:

Answers to Questions Posed by AEGL Committee Members on the Studies Conducted by Jappinen et al. (Brit. J. Ind. Med. 47, 824. 1990.) and Bhambhani et al. (J. Occup. Envr. Med. 39, 122. 1997; J. Occ. Envr. Med. 38, 1012. 1996; Am. Ind. Hyg. Assoc. J. 57, 464. 1996; Am. Ind. Hyg. Assoc. J. 55, 1030. 1994; J. Appl Phys. 71, 1872. 1991.)

NAC/AEGL-21

June 11-13, 2001

Individual #1

Question 1:

In all the Bhambhani et al. studies, the exposed individuals inhaled the H_2S through the mouth, as the route through the nose was blocked. In the Jappinen et al. study the exposed individuals were able to breathe through both the mouth and nose. Is there any significant difference in toxicological effects due to H_2S when inhaled only through the mouth compared to inhalation through both the nose and mouth?

Answer:

In the studies conducted by Bhambhani et al., the subjects breathed humidified air containing continuously-monitored concentrations of hydrogen sulfide.

During these studies the subjects breathed through the mouth only, making the throat a primary target for hydrogen sulfide exposure as there would be no removal by the nasal mucosa.

Therefore, mouth-only breathing maximizes the potential effect to the throat.

Individual #1

Question 2:

Is it possible to compare the amount of H_2S inhaled between the individuals exposed in the TNRCC study and the Jappinen et al./Bhambhani et al. studies? If so, please provide this comparison. It may help to add toxicological perspective to the two sets of data.

Answer:

If the respiration rate of the Texas workers is estimated as equal to the light activity reported in EPA's Exposure Factors Handbook, males in the Bhambhani studies inhaled approximately 10 times more hydrogen sulfide than did the Texas employees who reported symptoms.

Classifying the Texas employees breathing rates as moderate activity (as defined in EPA's Exposure Factors Handbook) suggests that the males in the Bhambhani studies inhaled about 4 times more than did any of the Texas employees.

(Also, in a personal communication, Bhambhani reported that the exhaled air from the exercising subjects had only a slight odor of hydrogen sulfide, suggesting nearly complete adsorption during his studies.)

Individual #2:

Question 1:

In the Jappinen et al. study only one concentration (2 ppm) of H_2S was used. This does not allow for the establishment of a dose-response relationship. Is it possible to analyze the data from the Jappinen et al. and Bhambhani et al. studies to establish any meaningful dose-response relationship for H_2S-generated health effects?

Answer:

Some of the human experimental studies utilized only one hydrogen sulfide exposure concentration. However, if the studies are analyzed together, the data are sufficient for derivation of AEGL-1 values ("weight of evidence" approach).

Reference	Subjects	Concentration	Duration	Effects
Jappinen et al., 1990	10 Asthmatics	2 ppm	30 minutes	headache (3/10); Increased airway resistance (8/10) with no accompanying clinical signs or effects on FVC, FEV_1, or FEF
Bhambhani & Singh, 1991	16 males, exercising to exhaustion	0.5 ppm 2.0 ppm 5.0 ppm	up to 16 minutes up to 16 minutes up to 16 minutes	no effects on respiratory function
Bhambhani et al., 1994, 1996a	13 males & 12 females, exercising to exhaustion	5 ppm	30 minutes	no effects on respiratory function
Bhambhani et al., 1996b	9 males & 10 females, exercising to exhaustion	10 ppm	15 minutes	no effects on respiratory function

In healthy humans exercising to exhaustion, no effects defined by AEGL-1 were noted at 5 ppm for 30 minutes or 10 ppm for 15 minutes.

In asthmatics, headache was noted in 3/10 individuals and increased Raw was measured in 8/10. However, the increase in Raw is judged to be of no clinical significance since no signs of a decrement in pulmonary function were noted.

Individual #2

Question 2:

How can the Jappinen et al. data be used to establish a basis for an AEGL-1 when the study's results are clearly above a lowest observable adverse effect level (30% incidence of headache and 20% incidence of bronchial obstruction) and appear to be above the threshold for AEGL-1 effects?

Answer:

While it is true that the effects observed in the Jappinen et al., study may be above the definition of AEGL-1, the study is well conducted in a sensitive (asthmatic) population. As is customary for derivation of values by the committee, appropriate modifying and/or uncertainty factors may be applied to the exposure values to derive AEGL-1 values as follows:

10-min	30-min	1-hr	4-hr	8-hr	
0.25 ppm	0.20 ppm	0.17 ppm	0.12 ppm	0.11 ppm	2 ppm for 30 minutes, Headache, and increased Raw and decreased conductance (not clinically significant in the absence of a decrement in pulmonary function) in asthmatics MF = 3 (effects above AEGL-1 definition) UF = 3 (wide variability of response suggested by total data base) n = 4.36

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Use of RD_{50} Data for Development of AEGLs

NAC / AEGL Committee Meeting
Washington, DC

June 11-13, 2001

Attachment 12

ExxonMobil Biomedical Sciences, Inc.

ExxonMobil

Why We Should Not Use 0.03 RD_{50}?

- Empirical
  - Original proposal was 0.01 - 0.1 x RD50
  - Based on correlation with OELs, not with human irritancy data
  - Other endpoints may have driven the OEL
- Does not consider the rate of response, mixed responses, or slope of the concentration-response curve
- Does not consider known species differences (rata vs. mouse)
- NAC / AEGL can / should determine appropriate chemical specific UFs

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Evaluation of RD_{50} Data for AEGL Development

- Rate of response
  - Most sensory irritants produce immediate response-maximum RR ⬇ in 1 min; e.g. SO_2
  - Other chemicals may produce delayed response (hrs); e.g. isocyanates or no clear maximum
- Mixed responses
  - Pulmonary and sensory irritation
- Concentration - response
  - If shallow slope, may need large UF, if steep, may need smaller UF
- Grading of responses observed at selected concentrations (ASTM)
  - <12% not biologically significant, 12-20% slight, 20-50% moderate, 50-85% extreme

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Evaluation of RD_{50} (cont'd)

- Species differences
  - Mice approximately 3x more sensitive than rats
  - Some strain differences in mice; $SWOF_1$ more sensitive than SW, CF1, and $B6C3F_1$
  - Where do humans fall?
- Individual differences
  - Very little difference amongst responses in inbred test animals
  - Variability in human clinical studies generally 2-5 x (Reference NAC / AEGL paper)

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Outline

- Background information on sensory irritation
- Standard test method for estimating sensory irritation potential of airborne chemicals (ASTM E981-84)
- Applications for development of AEGLs

ExxonMobil

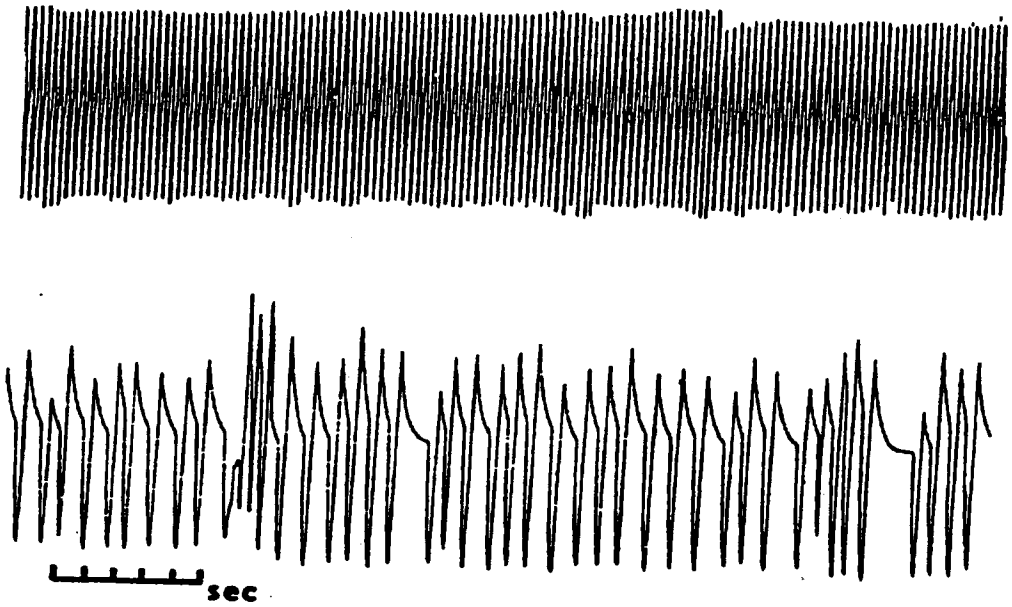
Classification of Chemical Irritants (Alarie)

- Sensory irritants
- Pulmonary irritants
- Bronchoconstrictors
- Respiratory irritants

ExxonMobil

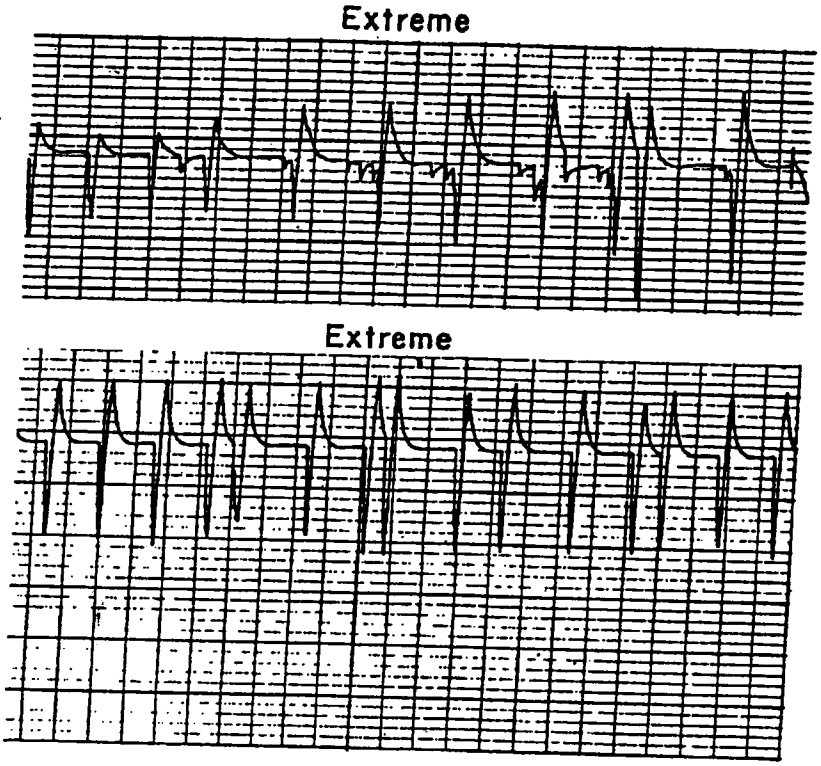
Physiological Effects Resulting from Sensory Irritation

- *Decreased breathing rate*
- *Increase in duration of expiration*
- Transient increase in respiratory rate
- Spasms of the larynx and bronchi
- Increase in the bronchial tone
- Decrease in pulmonary ventilation
- Decrease in pulse rate
- Increase in blood pressure
- Decrease in pulmonary blood flow



—Taken from Ref. (3).

FIG. 1 Typical Tracing of Normal Mouse Respiration (Top), and of a "Moderate" Sensory Irritant Response (Bottom)



TE 1—Decreases in respiratory rate of 50 to 85 % are graded as extreme responses.
TE 2—Taken from Ref. (1).

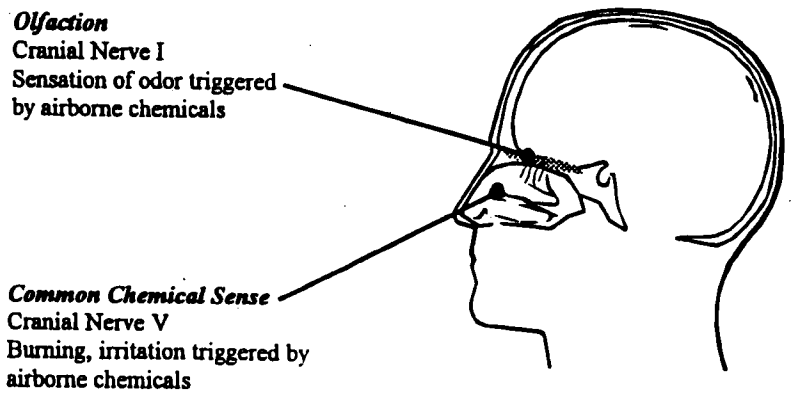
FIG. 9 Typical Tracings with Intensity of the Reaction Graded as Extreme

ExxonMobil

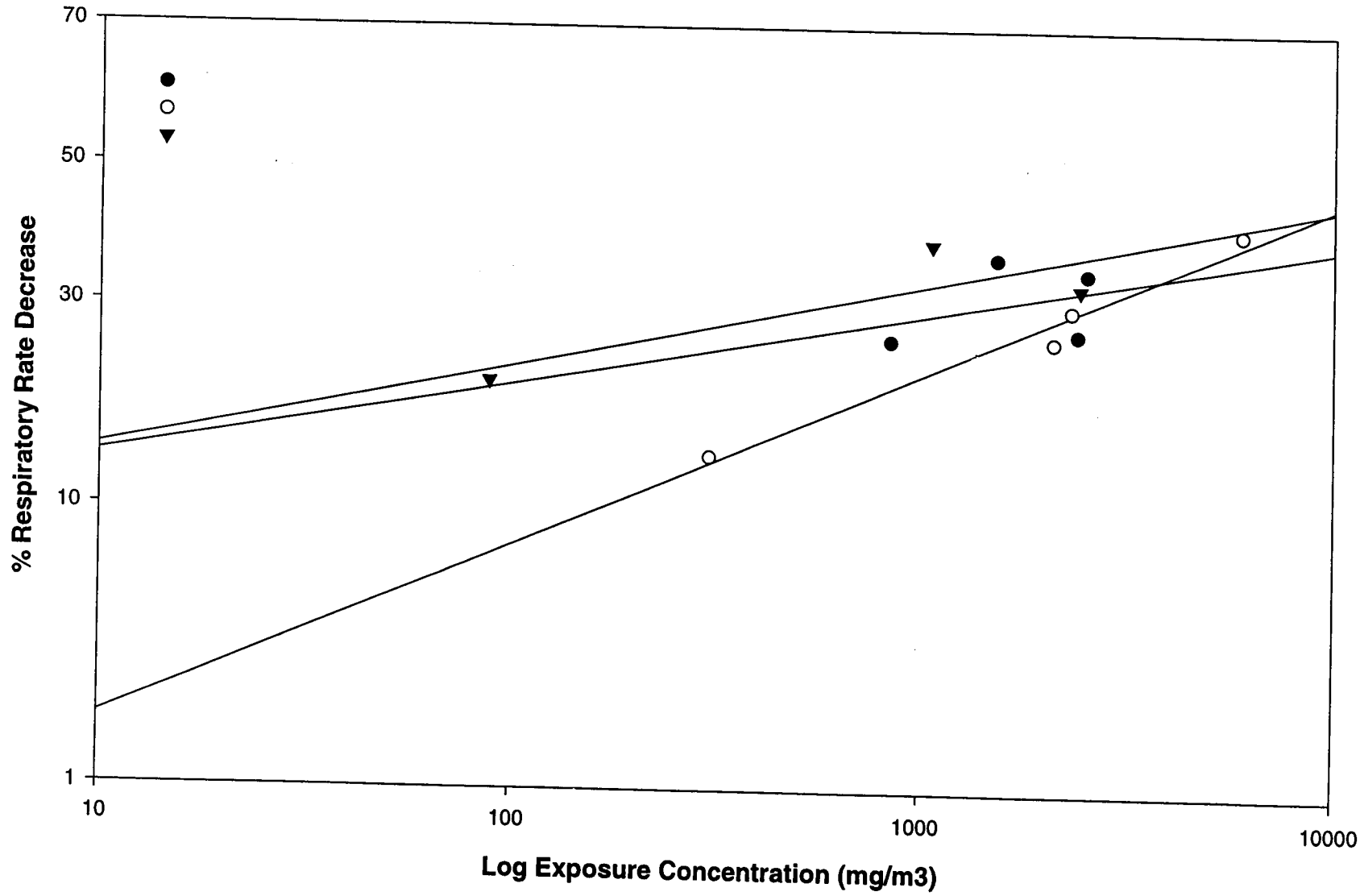
Sensory Irritation (Common Chemical Sense) Vs. Olfaction

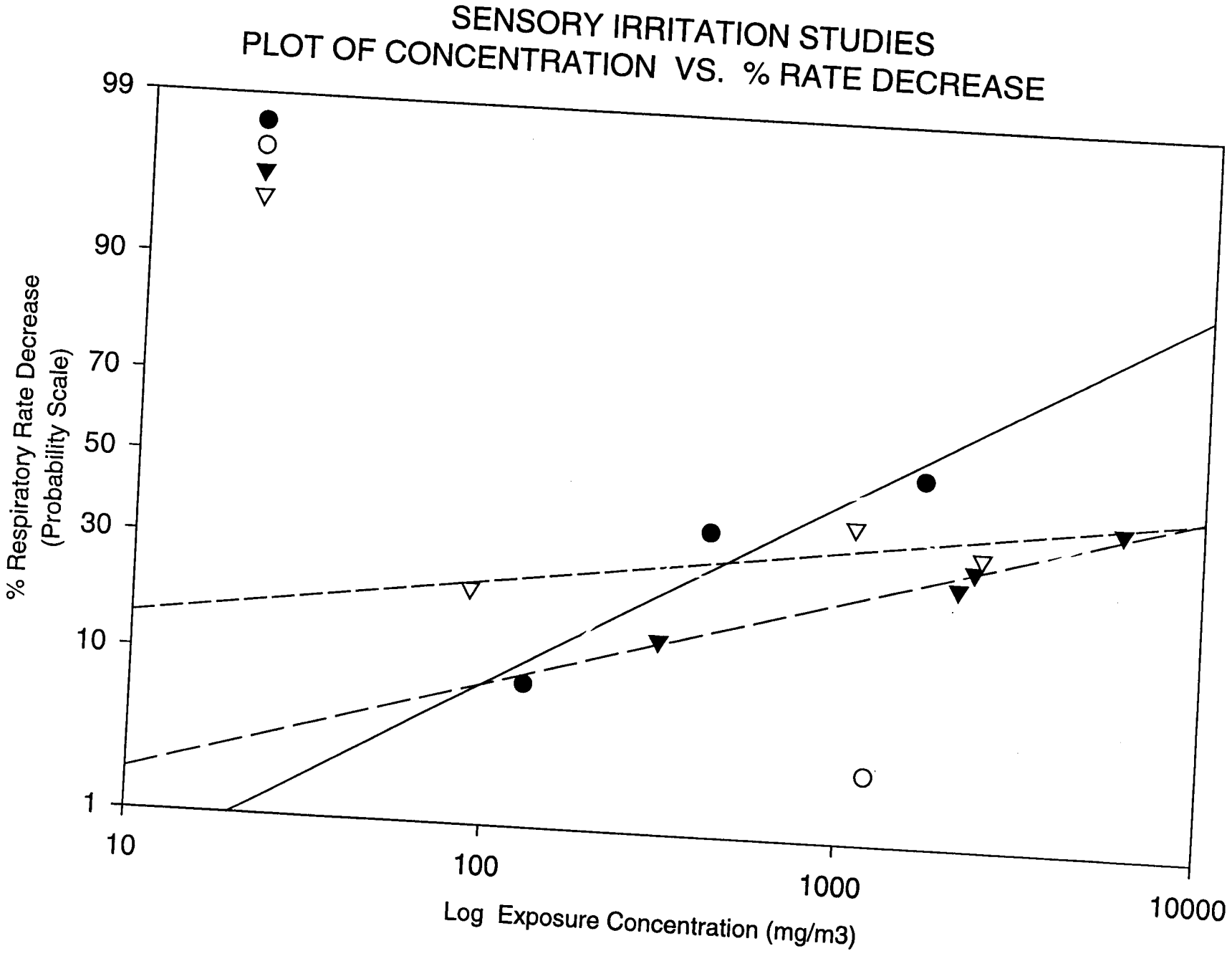
	Sensory Irritation	Olfaction
Mediating Nerve Receptors	Trigeminal (Cranial Nerve V) Free nerve endings in cornea, conjunctiva, nasal mucosa, mouth	Olfactory (Cranial Nerve I) Specialized nerve endings in the upper rear part of the nasal calvity
Anatomical Location of Receptors	Below the epithelium	In the epithelium
Mechanistic Considerations	Neurogenic inflammation (vasodilation, edema) mediated by release of neuropeptides such as substance P	Stimulation of mucous-embedded cilia of the olfactory neurons; 3 proteins presumably involved; Olfactory marker, binding, and specific proteins
Sensations	Burning, prickling, tingling, stinging, nose, eye throat irritation	Sense of smell

Figure 1

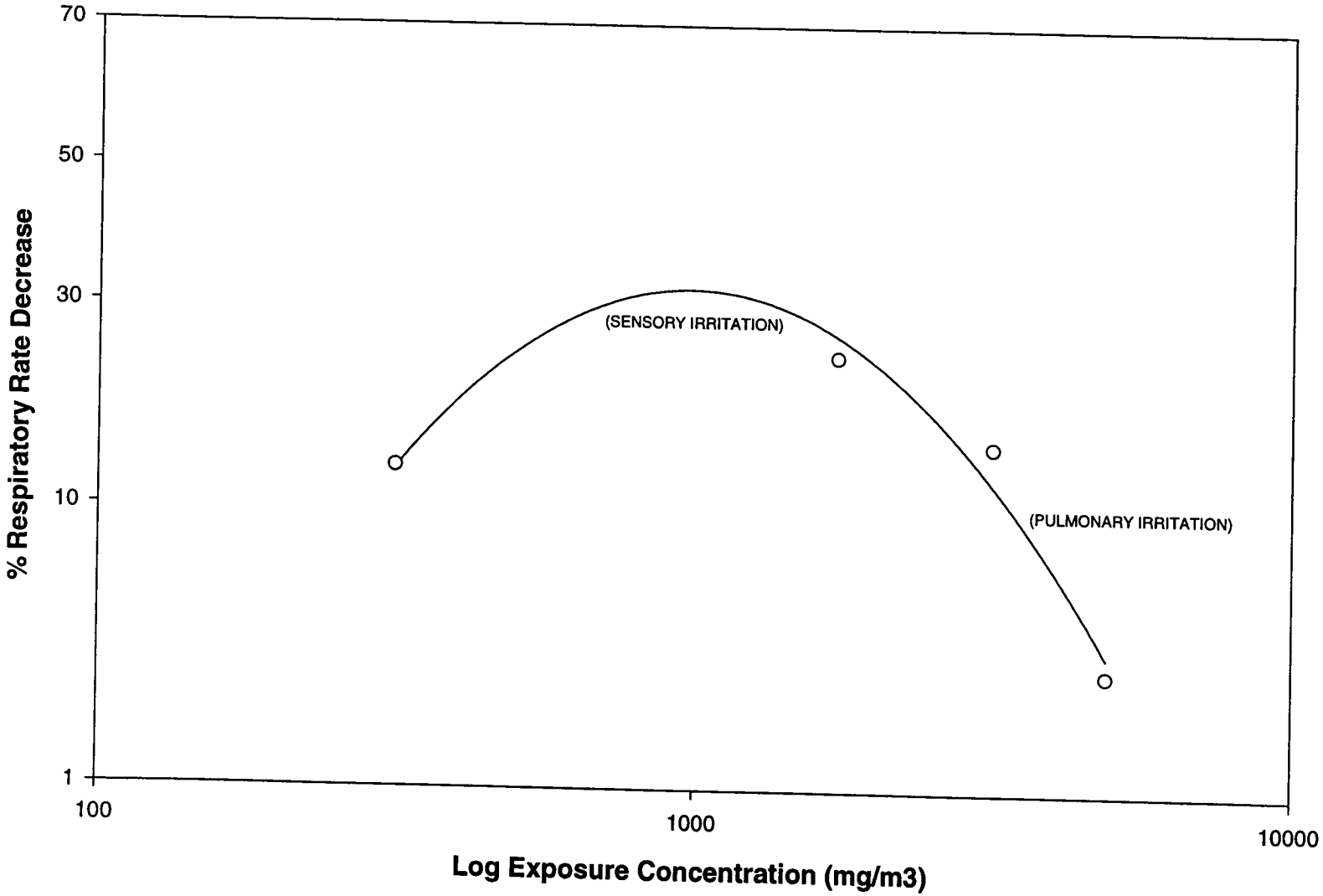

Olfaction
Cranial Nerve I
Sensation of odor triggered by airborne chemicals
Common Chemical Sense
Cranial Nerve V
Burning, irritation triggered by airborne chemicals

SENSORY IRRITATION STUDIES

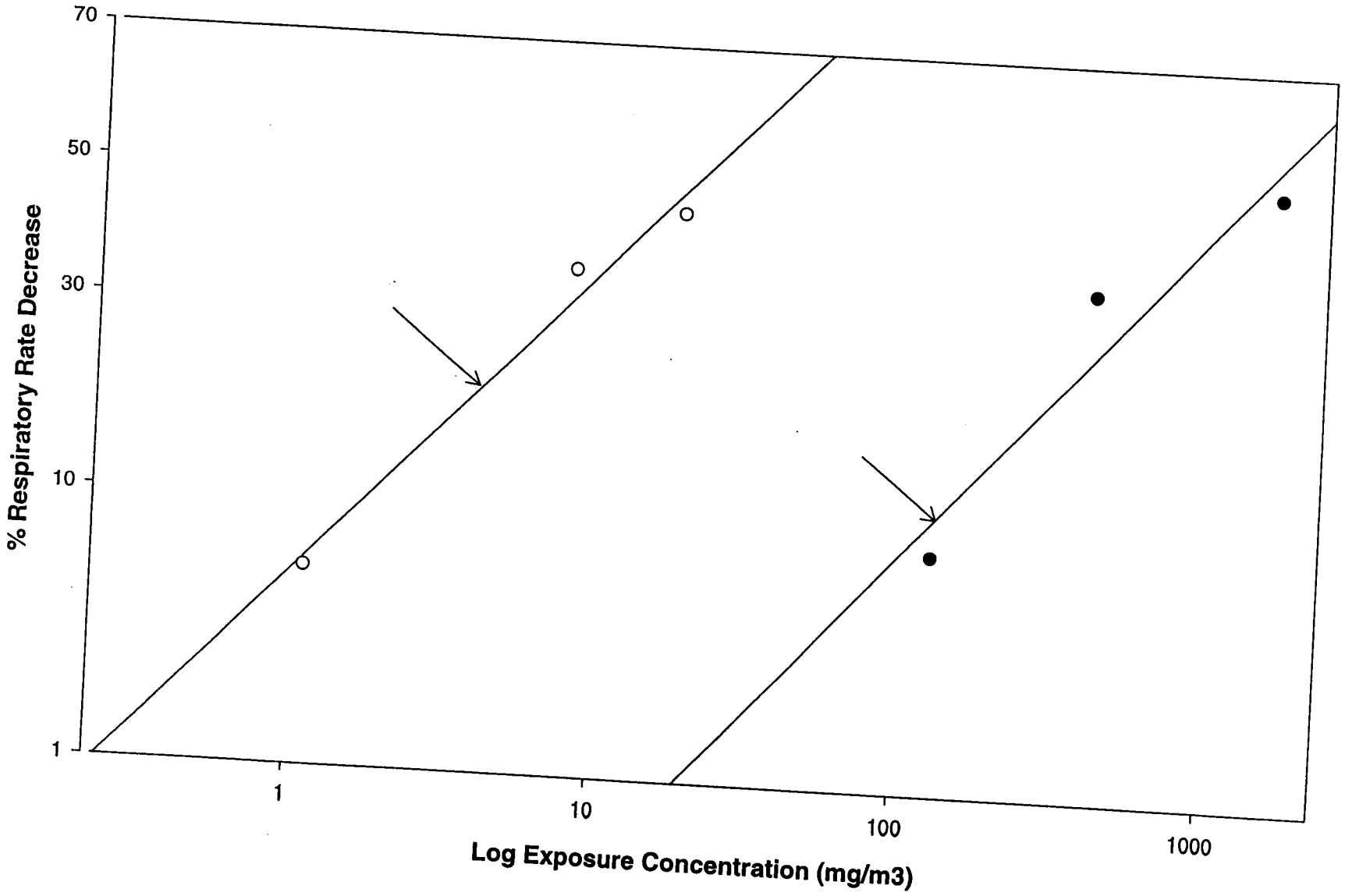


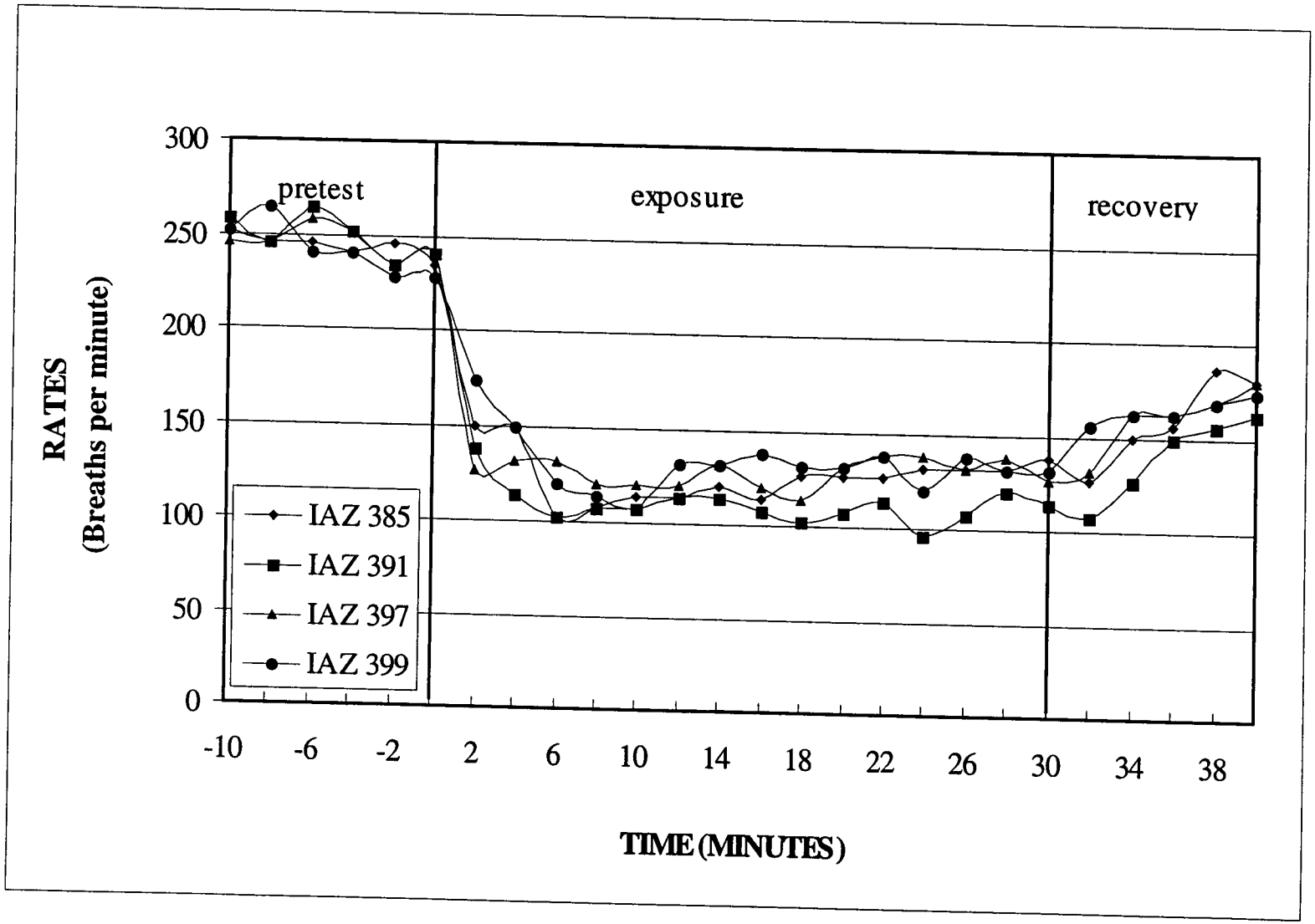

SENSORY IRRITATION STUDIES
PLOT OF CONCENTRATION VS. % RATE DECREASE
% Respiratory Rate Decrease
(Probability Scale)
99
90
70
50
30
10
1
10
100
1000
10000
Log Exposure Concentration (mg/m3)

SENSORY IRRITATION STUDIES

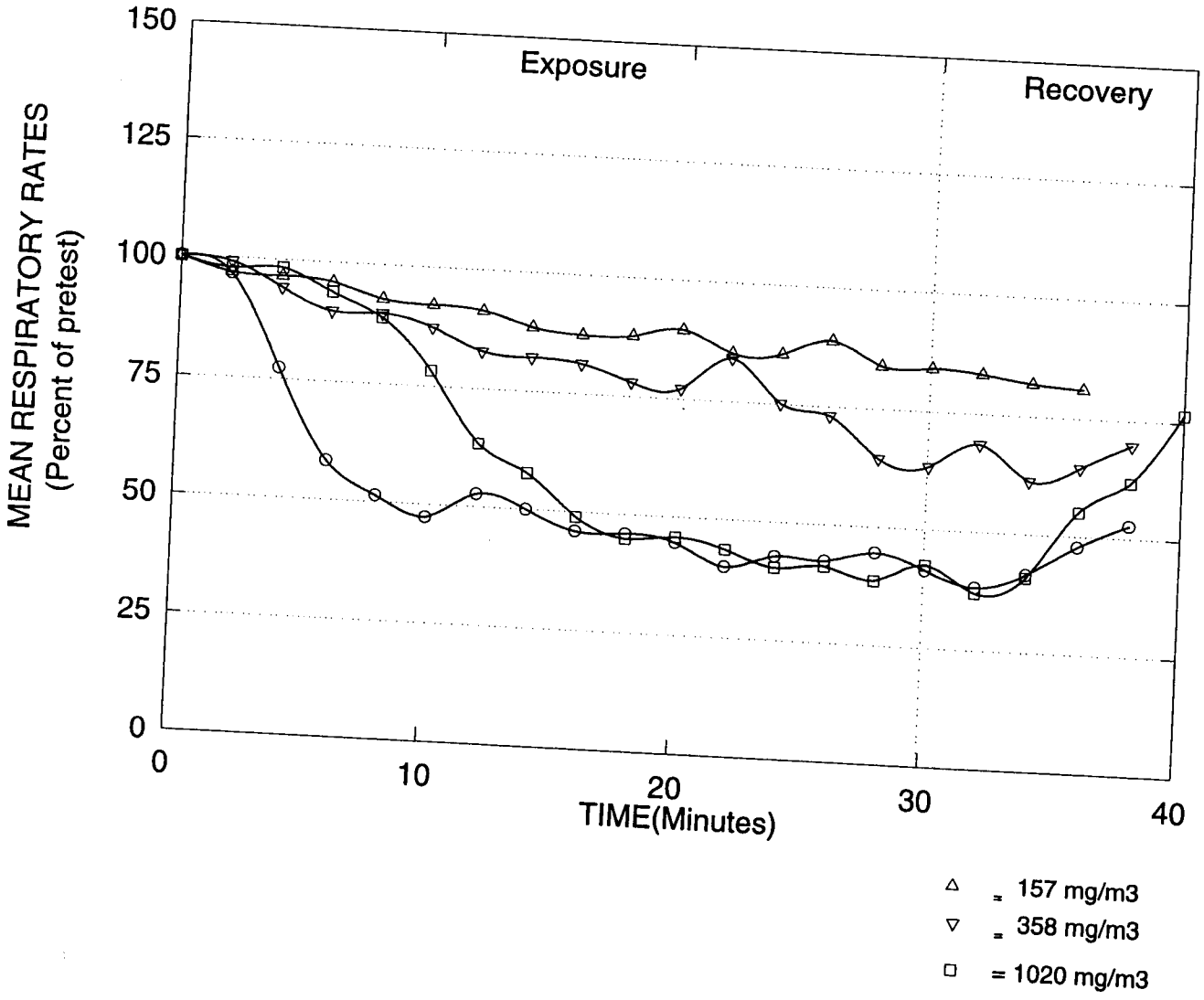


SENSORY IRRITATION STUDIES




300
250
200
150
100
50
0
pretest
exposure
recovery
IAZ 385
IAZ 391
IAZ 397
IAZ 399
-10
-6
-2
2
6
10
14
18
22
26
30
34
38
RATES
(Breaths per minute)
TIME (MINUTES)

100251 - SENSORY IRRITATION OF 2,3-DIBROMOPENTANE (MRD-94-002) IN MICE



U.S. AIR FORCE

JET FUEL VS ALARIE ASSAY

Application of ASTM Standard Method
E 981-84 to

"The Comparative and Quantitative Characterization of JP-8's Potential for Respiratory Irritation"

John P. Hinz
AFIERA/RSRE
Brooks AFB, TX

AGENDA

- Program Origins
- Outline of ASTM Standard Method E981-84, (Re-approved 1996)
- Jet Fuel Protocol and Study Design

PROGRAM ORIGINS

- Drivers
  - USAF/DoD program to replace JP-4 w JP-8
    - Health & safety concerns develop from flight line exposure
    - Irritation potential a critical data gap
  - NAC-AEGL targets JP-8 for review
    - USAF briefing on current JP-8 research program, Mar 99
    - Committee suspends deliberations - recommends AF include irritancy (Alarie) studies to address data gap
- Response
  - AF/A/N design jet fuel studies - ASTM E981-84
  - Studies under contract, under way w ExxonMobil lab

ASTM Standard Method E981-84

- Based on Alarie research 1966-82
- Quantitative measure of irritancy - reflex inhibition of respiration
- Describe dose-response curve - exposure concentration(s) vs breathing rate(s)
  - Alternative, single level for comparative study
- Calculate concentration that causes 50% reduction in breathing rate (RD_{50})
- Uses: id respiratory irritants, comparative ranking, determining prospective OELs, eye irritation

E981-84 Requirements

- Calibrated apparatus specific for this assay
  - Glass chamber, plethysmograph assembly, transducers with automated data capture, test atmosphere generation and measurement systems, flow control
- Test system
  - Swiss-Webster mice: males weighing 22-28 gms
- Duration
  - Standard: 30 min; Range: 3-180 min
- Operations
  - Adequate/controlled flow, prompt equilibration, consistent generation and measurement/characterization of atmosphere
- Response
  - Significant if decrement =/> 12%, based on pre-test breathing rate

JET FUEL STUDIES

"Quantitative And Comparative Characterization Of The Potential Of Various Jet Fuels To Cause Respiratory Tract Sensory Irritation"

- Study design guided by ASTM Method E981-84, standard industry protocol, current and applicable GLPs
- Characterize and compare the RD_{50} of three jet fuels --
  - JP-4: previous jet fuel - reference for these three fuels, volatile, vaporized - max attainable up to 1/2 LEL.
  - JP-8: "universal" fuel - reference for all subsequent fuel studies, less volatile, aerosolized - mixed atmosphere.
  - JP-8+100: JP-8 w enhanced thermal stability, 2° reference, comparable to JP-8.

JET FUEL STUDIES

- Phase I studies executed - JP-4, JP-8, JP-8+100
  - Operations, test atmosphere generation and analytical procedures meet or exceed E981-84 requirements, including
    - monitor and analyze all exposures - stability, vapor and aerosol
    - 3 samples/exposure - analysis by GC for THC & fingerprint
    - particle size - once per fuel + GC analysis
  - Draft report and raw data subject to audit - QA, then by AF/A/N
  - Preliminary data suggests JP-8 may be 2X as irritating as JP-4
- Phase II studies planned - 5 more fuels
  - JP-5, JP-7, JP-TS, JP-10, light marine diesel
  - Single level, comparative study targeted at JP-8's RD_{50}
  - Operational and analytical requirements comparable to Phase I

JET FUEL STUDIES

- Current plans
  - Contract Phase II
  - EMBSI to complete Phase I report
  - Army, Navy, Air Force to review and comment
  - Present Phase I results at Jet Fuel Conference - Aug 01
  - As promised in Mar 99, return to NAC-AEGL w Phase I results + Conference proceedings in hand
    - **SAN ANTONIO, DEC 01**

THE RELATIVE SUSCEPTIBILITY OF CHILDHOOD ASTHMATICS AND ADULT ASTHMATICS TO ACUTE EXPOSURES OF IRRITANT CHEMICALS

INTENT:

Reach consensus or majority opinion on the NAC Committee's position on this matter for presentation at the NAS meeting on August 29, 2001.

OUTLINE:

1. **The issue**
2. **What is asthma**
3. **AEGL-1 effect intraspecies uncertainty factors**
4. **AEGL-2 effect intraspecies uncertainty factors**
5. **AEGL-3 effect intraspecies uncertainty factors**
6. **Conclusions on AEGL-1,2, and 3 intraspecies UF**
7. **Childhood asthmatic susceptibility to irritant exposure relative to adult susceptibility**
8. **Use of key and supporting data to develop intraspecies UFs**
9. **Final conclusions**
10. **Discussion**
11. **Consensus building**

THE ISSUE

Are normal children more susceptible than normal adults to exposure to irritant gasses?

Are asthmatic children or adolescents more susceptible than adult asthmatics to exposure to irritant gasses?

A definitive answer to this question requires specific data sets which would allow comparisons between:

1) - healthy children and healthy adults

2) - asthmatic children and asthmatic adults

Who have been:

1) - exposed to a range of concentrations of irritants sufficient to determine a threshold for:

2) - a specific type and level of response which is physiologically significant.

ASTHMA-DEFINITION

Asthma has been described by the Second Panel on the Management of Asthma (NIH, 1997) as a

"chronic inflammatory disorder of the airways."

This inflammation contributes to airway hyper-responsiveness, airflow limitation, respiratory symptoms, and disease chronicity.

ASTHMA-CHARACTERIZATION OF SUBJECTS

ASTHMA SEVERITY (NIH, 1997)			
STEP	Symptoms	Nighttime symptoms	Lung function
4 Severe persistent	-Continual symptoms -Limited physical activity -Frequent exacerbations	Frequent	-FEV_1 or PEF ≤ 60% predicted -PEF variability > 30%
3 Moderate persistent	-Daily symptoms -Daily use of inhaled short-acting $beta_2$-agonists -Exacerbations affect activity -Exacerbations ≥ 2 times a week; may last days.	> 1 time a week	-FEV_1 or PEF > 60% - < 80% predicted -PEF variability >30%
2 Mild persistent	-Symptoms >2 times a week but < 1 time a day -Exacerbations may effect activity	> 2 times a month	-FEV_1 or PEF ≥ 80% predicted -PEF variability < 20%
1 Mild intermittent	-Symptoms ≤ 2 times a week -Asymptomatic and normal PEF between exacerbations -Exacerbations brief (from a few hours to a few days); intensity may vary	≤ 2 times a month	-FEV_1 or PEF ≥ 80% predicted -PEF variability < 20%

RELATIVE SUSCEPTIBILITIES OF HEALTHY AND ASTHMATIC INDIVIDUALS BY AEGL LEVEL

AEGL-1
DISCOMFORT

-Bronchoconstriction

-Chamber studies exist on human healthy and asthmatic adults and adolescents

AEGL-2
DISABILITY
IMPAIRMENT OF ESCAPE

-Bronchoconstriction
-Edema

-No chamber studies on humans
-Animal studies exist-usually on edema or histopathology as an endpoint
-No good animal models for asthma

AEGL-3
DEATH

-Bronchoconstriction
-Edema

-No chamber studies on humans
-Animal studies exist-usually on edema or histopathology as an endpoint
-No good animal models for asthma

AEGL-1 DISCOMFORT

Are normal children more susceptible than normal adults to exposure to irritant gasses?

Are asthmatic children or adolescents more susceptible than adult asthmatics to exposure to irritant gasses?

A definitive answer to this question requires specific data sets which would allow comparisons between:

~~1) - healthy children and healthy adults~~

~~2) - asthmatic children and asthmatic adults~~

Who have been:

~~1) - exposed to a range of concentrations of irritants sufficient to determine a threshold for:~~

~~2) - a specific type and level of response which is physiologically significant.~~

AEGL-1 DISCOMFORT

Data set do exist which allow some comparisons between:

1) - Healthy adults and adolescents and

2) - Asthmatic adults and adolescents

Who have been:

1) - exposed to a range of concentrations of irritants sufficient to determine a range in which humans begin to respond to irritant exposure:

2) - a specific type and level of response which is measurable but not always physiologically significant:

- **Airways resistance (SRaw) increases**
- **FEV_1 decrements**
- **Symptoms**

-Exercising (to varying degrees) and non-exercising
-Breath through mouthpiece or full face

AEGL-1 DISCOMFORT

Table 3 -page 23

Summary of Comparative Irritant Responses
In Healthy Versus Potentially Susceptible Subjects

Chemical	Estimated Threshold in Healthy Subjects[1]	Estimated Threshold in Susceptible Subjects[1]	Estimated Differential Response Factor	Susceptible Group
Chlorine	1.0 (P) 1.0 (S)	0.5 (P) 0.5 (S)	2	Asthmatics, history of allergic rhinitis
Formaldehyde	≥3 (P^3) 2 (S)	>3 (P) <3 (S)	1?	Asthmatics
Hydrogen chloride		>1.8 (P, S)	?	Asthmatics
Hydrogen sulfide	>10 (P)	>2 (P) 2 (S)	?	Asthmatics
Nitrogen dioxide	0.2-0.3???4 (P)	1.0 (P)	3-5 or less ??????	Asthmatics
Ozone	0.25 ($P)^2$	0.12 P^2 <0.24 P >0.25 0.12	1.5 1.0 1.0 1.5 1.0	Asthmatics COPD Ischemic heart dis. African American Gender
Sulfur dioxide	0.75 (P)	0.4 (P)	2-3	Asthmatics; substantial variation in asthmatic group observed
Sulfuric acid	500 ug/m	400 ug/m^3 68 ug/m^3 [4](??? significance)	1.3-7 or maybe 1.3	Adult asthmatics Adolescent asthmatics

[1]Value are in ppm unless otherwise specified
[2]For exposure durations of <3hr
[3]Nasal flow resistance
[4]Exposure was by mouthpiece
P: Pulmonary function
S: Symptoms

AEGL-1 DISCOMFORT

For irritant gasses the difference in response between healthy and asthmatic individuals is on the order of 1-5 fold.

AEGL-2 DISABILITY OR IMPAIRMENT OF ESCAPE

AEGL-2
DISABILITY
IMPAIRMENT OF ESCAPE

-Bronchoconstriction
-Edema

-No chamber studies on humans
-Animal studies exist-usually on edema or histopathology as an endpoint
-No good animal models for asthma

AEGL-2 DISABILITY OR IMPAIRMENT OF ESCAPE

SELECTION OF INTRASPECIES UNCERTAINTY FACTOR

The selection of uncertainty factors in deriving AEGL-2 levels for irritants will require a chemical specific analysis of all of the data. This will require careful assessment of the following considerations:

1) Which intraspecies uncertainty factor (1, 3, or 10), when applied to the key study, gives the best fit with all of the other data on the chemical or its analogs? Are the derived AEGL values consistent with the supporting data?

AEGL-2 DISABILITY OR IMPAIRMENT OF ESCAPE

2) If the AEGL value generated by the use of a higher intraspecies uncertainty factor is not reasonable in light of the supporting data, what is the reason?

a) Was an adverse effect used to determine an AEGL-2 level which is far below that expected for an AEGL-2 endpoint. For example, selection of mild coughing as an AEGL-2 endpoint. Why was that endpoint conservative or below the endpoint effect? In this case a lower uncertainty factor may be justified.

b) The use of a higher uncertainty factor drives the AEGL-2 value to a level at or below a level which humans have been shown to tolerate as a result of human exposure or monitoring studies.

c) The use of a higher uncertainty factor would have driven the AEGL-2 value to a level which is not supported by the supporting data, especially as they relate to the human experience.

AEGL-2 DISABILITY OR IMPAIRMENT OF ESCAPE

d) Are the dose response curves in the animal studies exceptionally steep? For example, if the dose which just initiates a measurable amount of edema is close to the dose which causes death, this may justify a lower uncertainty factor. The irritant chemical stimulates or injures lung tissue by means of a non-specific chemical reaction in the cell. This reaction should be similar in asthmatic and healthy individuals. An extremely steep dose response curve described above (from the beginning of lung edema to death) would argue for the conclusion that the difference in concentration between beginning to react with, injure, and in some cases destroy, lung tissue and the concentration that results in death is a very narrow range. One might argue that, although the asthmatic individual might react with pulmonary edema formation and/or inflammatory reaction at the lower end of that range, the range itself is so narrow that the difference between the asthmatic reacting and the healthy person reacting is minimal. When drawing this conclusion is important to have good pathology data on the lung as well as mortality data.

e) Other considerations that may be chemical-specific or data-specific that support the conclusions drawn to strengthen the rationale used.

3) Considering interspecies and intraspecies uncertainty factors independently can lead to an overly conservative AEGL value. When the two uncertainty factors are multiplied together the resultant total uncertainty factor generally represents a worst case times a worst case. Therefore at the total uncertainty factor must be evaluated and the AEGL values compared with all of the supporting data. If the supporting data do not support the AEGL values it may be necessary to decrease one or both of the uncertainty factors using the supporting data as a rationale.

4) Give specific data to support the conclusions drawn to strengthen the argument made.

AEGL-3 DEATH

SAME ARGUMENTS AND RATIONALE AS FOR THE AEGL-2 ENDPOINT

INTRASPECIES UNCERTAINTY FACTOR FOR EXPOSURES TO IRRITANT GASSES

CONCLUSIONS

AEGL-1

- DATA EXIST FOR AEGL-1 TIER EFFECTS WHICH INDICATE THRESHOLD CONCENTRATIONS TO WHICH ASTHMATIC SUBJECTS RESPOND RANGE FROM 1 TO 5-FOLD LOWER THAN HEALTHY INDIVIDUALS

- CONSEQUENTLY, THE NAC/AEGL COMMITTEE GENERALLY APPLIES AN UNCERTAINTY FACTOR OF 3 TO DATA FROM HUMAN STUDIES WHICH COMPRISE HEALTHY INDIVIDUALS BUT NO ASTHMATIC TEST SUBJECTS IN DERIVING AEGL-1 VALUES.

CONCLUSIONS

AEGL-2 AND AEGL-3

- THERE IS A LACK OF DATA TO ADDRESS DIFFERENCES IN RESPONSE THRESHOLDS FOR IRRITANT CHEMICALS BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS FOR AEGL-2 AND AEGL-3 TIER EFFECTS.

- FOR MANY CHEMICAL IRRITANTS, THE UNCERTAINTY FACTOR OF 3 USED FOR AEGL-1 EFFECTS HAS BEEN USED TO DERIVE AEGL-2 AND AEGL-3 VALUES. THE RATIONALE GENERALLY HAS BEEN THE FACT THAT THE IRRITANTS ARE DIRECT ACTING AND THAT THEIR EFFECT IS NOT LIKELY TO VARY AMONG INDIVIDUALS, INCLUDING SUSCEPTIBLE INDIVIDUALS. HOWEVER, IN THESE INSTANCES, THE DERIVED AEGL-2 VALUE HAS OFTEN BEEN EVALUATED WITHIN THE CONTEXT OF ALL OTHER SUPPORTING DATA TO FURTHER VALIDATE THE SELECTION.

CONCLUSIONS

AEGL-2 AND AEGL-3

- IN THE ABSENCE OF DIFFERENTIAL RESPONSE DATA BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS AT THE AEGL-2 AND AEGL-3 TIER, AND THE EXISTENCE OF HUMAN DATA INDICATING A 1 TO 5-FOLD RANGE OF DIFFERENCES FOR LESSER ADVERSE EFFECTS, AN INTRASPECIES UNCERTAINTY FACTOR OF 3 WILL BE USED AND EVALUATED WITHIN THE CONTEXT OF OTHER SUPPORTING DATA TO FURTHER VALIDATE THE SELECTION. THIS IS SUPPORTED FURTHER BY THE ABSENCE OF INDIRECT EVIDENCE SUCH AS THE MODES OR MECHANISMS OF ACTION OF IRRITANTS OR THE BIOCHEMICAL/PHYSIOLOGICAL DETAILS OF CHEMICALLY-INDUCED ASTHMATIC ATTACKS THAT MIGHT PROVIDE INSIGHT INTO RESPONSE DIFFERENCES BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS AT THE AEGL-2 TIER. IN INSTANCES WHERE SUPPORTING DATA SUGGEST AN INTRASPECIES UNCERTAINTY FACTOR OF 3 IS INADEQUATE, AN UNCERTAINTY FACTOR OF 10 MAY BE USED.

CHILDREN ASTHMATIC VS ADULT ASTHMATIC SENSITIVITY TO IRRITANT EXPOSURE

REASONS FOR POTENTIAL CONCERN:

-15 million Americans have asthma
- -5 million are children
- -higher percentage of children have asthma compared to adults

-Children asthmatics are hospitalized at a frequency of 2-3 times more than adults

-Children:
- - have smaller airways
- - on a mg/kg basis children breath in about twice as much air as an adult
- -children have less smooth muscle mass around the bronchii

-Confounding factors to assessing the relative sensitivity of children and adults
- -confounding medical, social and behavioral factors are difficult to separate from true differences in incidence of hospitilization
- -less smooth muscle means less severe constriction of airways
- -surface area of the lungs, scrubbing differences and metabolic rate may act against the higher dose received from a greater volume breathed per mg of body weight

CHILDREN ASTHMATIC VS ADULT ASTHMATIC SENSITIVITY TO IRRITANT EXPOSURE

Are asthmatic children or adolescents more susceptible than adult asthmatics to exposure to irritant gasses?

A definitive answer to this question requires specific data sets which would allow comparisons between:

1) - healthy children and healthy adults

2) - asthmatic children and asthmatic adults

Who have been:

~~**1) - exposed to a range of concentrations of irritants sufficient to determine a threshold for:**~~

2) - a specific type and level of response which is physiologically significant.

CHILDREN ASTHMATIC VS ADULT ASTHMATIC SENSITIVITY TO IRRITANT EXPOSURE

Avitol measured PC_{20} in children ages:
1-6 7-11 12-17
Mild, moderate, and severe in each group

PC_{20} = Concentration of methacholine required to reduce FEV_1 by 20%

The values for all age groups did not differ significantly within an asthma severity category but did between categories except for the moderate/severe in the 6-11 and 12-17 group although the PC_{20} was lower for the severe category in these age groups.

CHILDREN ASTHMATIC VS ADULT ASTHMATIC SENSITIVITY TO IRRITANT EXPOSURE

de Pee et al., 1991 measured the plateau of the reduction of FEV_1 upon methacholine challenge in health and asthmatic individuals from 7-47 years of age. This was plotted against the PC_{20}.

Child asthmatics do not differ from adult asthmatics and non-asthmatic children do not respond differently from non-asthmatic adults when methacholine sensitivity is compared to maximal airway narrowing.

CHILDREN ASTHMATIC VS ADULT ASTHMATIC SENSITIVITY TO IRRITANT EXPOSURE

London episode of December 1952

DEATHS IN LONDON ADMINISTRATIVE COUNTY BY AGE							
All	<4 weeks	4 weeks-1 year	1-14 years	15-44 years	45-64 years	65-74 years	75+ years
Week before the episode							
945	16	12	10	61	237	254	335
Week after the episode							
2484	28	26	13	99	652	717	949
Factor by which deaths were increased							
2.6	1.75	2.2	1.3	1.6	2.8	2.8	2.8

The increase in death rate from the pollution episode ranged from 1.3 for 1-14 year old children to 2.8 for 45-75+ years of age. The greatest increase is for those over 45 years of age with the greatest difference in susceptibility of approximately 2-fold. The exposure was to all age groups, sexes, and individuals of varying degrees of susceptibility and to very similar levels and durations of exposure. The increase in death rate was clearly due to an acute episode. If children represented a particularly susceptible group then their death rate increase should have been much greater than adults. Since this was not the case, children do not seem to be at greater risk of death than adults when exposed to high levels of pollutants.

USE OF KEY AND SUPPORTING DATA TO DERIVE AN INTRASPECIES UNCERTAINTY FACTORS FOR AEGL VALUES

Hydrogen chloride

The AEGL values for hydrogen chloride were developed using an intraspecies uncertainty factor of 1 for the AEGL-1 values and 3 for the AEGL-2 and 3 values.

Summary of Proposed AEGL Values For Hydrogen Chloride[ppm (mg/m^3)]						
Classification	10-min.	30-min.	1-hr.	4-hr.	8-hr.	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	1.8 (2.7)	No-adverse-effect-level in exercising human asthmatics (Stevens et al., 1992)
AEGL-2 (Disabling)	100 (160)	43 (65)	22 (33)	5.4 (8.1)	2.7 (4.1)	Mouse RD_{50} (Barrowet al, 1977); Histopathology in rats (Stavert et al., 1991)
AEGL-3 (Lethality)	620 (940)	210 (310)	100 (160)	26 (39)	13 (19)	Estimated NOEL for death from 1-Hour rat LC_{50} (Wohlslagel et al., 1976; Vernot et al., 1977)

AEGL-1 RATIONALE

Since the test subjects were exercising asthmatics who are considered to be the susceptible population and the endpoint was essentially a no-effect-level which was below the AEGL-1 threshold, no uncertainty factor has been applied to account for susceptible human subpopulations.

USE OF KEY AND SUPPORTING DATA TO DERIVE AN INTRASPECIES UNCERTAINTY FACTORS FOR AEGL VALUES

AEGL-2 RATIONALE Page 40

Interspecies UF=3

Rodent data used to set AEGL-2 and
Rodent less susceptible than primate

Modifying factor=3

Sparse data base

Intraspecies UF=3

TOTAL UF=30

-If an intraspecies UF of 10 were used the total UF would drive the 4 hour AEGL-2 value below the NOEL observed in an exercising asthmatic exposed to 1.8 ppm for 45 minutes which was the level set across 8 hours for the AEGL-1

-The value of n=1 is based upon lethality data from 1 to 100 minutes so it is a reasonable value

-The 30 minute AEGL-2 value of 43 ppm is reasonable because a 15 minute exposure of baboons to 500 ppm caused only slightly increased respiratory rate

-THEREFORE AN INTRASPECIES UNCERTAINTY FACTOR OF 3 IS THE MOST REASONABLE VALUE

USE OF KEY AND SUPPORTING DATA TO DERIVE AN INTRASPECIES UNCERTAINTY FACTORS FOR AEGL VALUES

AEGL-3 RATIONALE Page 41

Interspecies UF=3

Rodent data used to set AEGL-3 and
Rodent less susceptible than primate

TOTAL UF=10

- The steep dose-response curve for lethality observed in the Wohlslagel et al. (1976) study in which 1041 ppm (1/3 of the LC50 of 3124 ppm) was lower than the non-lethal dose of 1813 ppm. This is a conservative selection of the non-lethal dose and the steep dose-response curve argues for little inter-individual variability

- If an intraspecies uncertainty of 10 were used, the total uncertainty factor would be 30. AEGL-3 values generated from a total uncertainty factor of 30 would be close to the derived AEGL-2 values (within a factor of 2), in turn, these values are considered reasonable when compared with data on exercising asthmatics

- An interspecies uncertainty factor of 3 has already been applied to data from an animal which is less susceptible than primates, making that uncertainty factor conservative

USE OF KEY AND SUPPORTING DATA TO DERIVE AN INTRASPECIES UNCERTAINTY FACTORS FOR AEGL VALUES

AEGL-3 RATIONALE Page 41

- Sellakumar et al. (1985) exposed rats to 10 ppm of hydrogen chloride for 6 hours a day, 5 days a week for life and only observed increased trachael and laryngeal hyperplasia. The 360 minute AEGL-3 using an intraspecies uncertainty factor of 3 is 17 ppm, close to the level used in the lifetime study in a species less susceptible than primates in which only mild effects were induced

- Rats exposed to 50 ppm of hydrogen chloride for 6 hours per day, 5 days a week for 90 days (Toxigenics, 1984) exhibited mild rhinitis. This level is already 3-fold above the AEGL-3 value for death which was derived with an intraspecies uncertainty factor of 3.

- ALTHOUGH NO ONE FACTOR CONCLUSIVELY SUPPORTS THE USE OF AN INTRASPECIES UNCERTAINTY FACTOR OF 3, ALL OF THE FACTORS CONSIDERED ABOVE PROVIDE STRONG WEIGHT OF EVIDENCE SUPPORT TO THIS SELECTION.

CONCLUSIONS

1. CHILDHOOD ASTHMATIC SENSITIVITY

THERE ARE NO DATA TO SUPPORT THE CONCERN THAT CHILDHOOD ASTHMATICS ARE MORE SENSITIVE TO EXPOSURE TO IRRITANT GASSES THAN ADULT ASTHMATICS.

2. AEGL-1

DATA EXIST FOR AEGL-1 TIER EFFECTS WHICH INDICATE THRESHOLD CONCENTRATIONS TO WHICH ASTHMATIC SUBJECTS RESPOND RANGE FROM 1 TO 5-FOLD LOWER THAN HEALTHY INDIVIDUALS.

CONSEQUENTLY, THE NAC/AEGL COMMITTEE WILL GENERALLY APPLY AN UNCERTAINTY FACTOR OF 3 TO DATA FROM HUMAN STUDIES WHICH COMPRISE HEALTHY INDIVIDUALS BUT NO ASTHMATIC TEST SUBJECTS IN DERIVING AEGL-1 VALUES.

CONCLUSIONS

3. AEGL-2 AND AEGL-3

THERE IS A LACK OF DATA TO ADDRESS DIFFERENCES IN RESPONSE THRESHOLDS FOR IRRITANT CHEMICALS BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS FOR AEGL-2 AND AEGL-3 TIER EFFECTS.

FOR MANY CHEMICAL IRRITANTS, THE UNCERTAINTY FACTOR OF 3 USED FOR AEGL-1 EFFECTS HAS BEEN USED TO DERIVE AEGL-2 AND AEGL-3 VALUES. THE RATIONALE GENERALLY HAS BEEN THE FACT THAT THE IRRITANTS ARE DIRECT ACTING AND THAT THEIR EFFECT IS NOT LIKELY TO VARY AMONG INDIVIDUALS, INCLUDING SUSCEPTIBLE INDIVIDUALS. HOWEVER, IN THESE INSTANCES, THE DERIVED AEGL-2 VALUE HAS OFTEN BEEN EVALUATED WITHIN THE CONTEXT OF ALL OTHER SUPPORTING DATA TO FURTHER VALIDATE THE SELECTION.

CONCLUSIONS

3. AEGL-2 AND AEGL-3

IN THE ABSENCE OF DIFFERENTIAL RESPONSE DATA BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS AT THE AEGL-2 AND AEGL-3 TIER, AND THE EXISTENCE OF HUMAN DATA INDICATING A 1 TO 5-FOLD RANGE OF DIFFERENCES FOR LESSER ADVERSE EFFECTS, AN INTRASPECIES UNCERTAINTY FACTOR OF 3 WILL BE USED AND EVALUATED WITHIN THE CONTEXT OF OTHER SUPPORTING DATA TO FURTHER VALIDATE THE SELECTION. THIS IS SUPPORTED FURTHER BY THE ABSENCE OF INDIRECT EVIDENCE SUCH AS THE MODES OR MECHANISMS OF ACTION OF IRRITANTS OR THE BIOCHEMICAL/PHYSIOLOGICAL DETAILS OF CHEMICALLY-INDUCED ASTHMATIC ATTACKS THAT MIGHT PROVIDE INSIGHT INTO RESPONSE DIFFERENCES BETWEEN ASTHMATICS AND HEALTHY INDIVIDUALS AT THE AEGL-2 AND AEGL-3 TIER. IN INSTANCES WHERE SUPPORTING DATA SUGGEST AN INTRASPECIES UNCERTAINTY FACTOR OF 3 IS INADEQUATE, AN UNCERTAINTY FACTOR OF 10 MAY BE USED.

UNIVERSITY OF CALIFORNIA
LAWRENCE LIVERMORE NATIONAL LABORATORY

INSTITUTE OF HYGIENE, TOXICOLOGY AND
OCCUPATIONAL PATHOLOGY

SOUTH CENTER FOR MEDICAL ASSISTANCE UNDER CHEMICAL EMERGENCIES

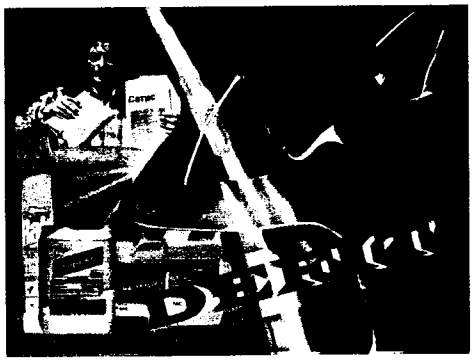
POISONING DIFFERENTIAL DIAGNOSTICS COMPUTER SOFTWARE SYSTEM

KAIF is an entirely new approach to diagnosing acute poisoning with chemical substances, which mainly afflict the nervous system.

KAIF is a system , DESIGNED TO CONSULT MEDICAL DOCTORS AND TO TRAIN MEDICAL STUDENTS

KAIF is a complex computer system, which includes two interrelated software programs: **DEFIT and NEUROTOPIC**

DEFIT is a computer program designed to recognize a chemical substance, which was a cause of acute poisoning and exposure of the nervous system.



As a basis for the DEFIT software program an earlier version was used, named FOND, which was created by the same authors (Russian Goverment certificates N 920042 of March 10, 1992 and N 003 of February 26, 1999 where issued and registered).

The DEFIT software program includes the following elements.

- *An entirely new mathematical chemicals recognition algorithm developed by the authors, which identifies chemical substances by their specific clinical features of poisoning ;*
- *It is oriented to and integrated with a database of poisoning cases with neurotropic substances.*

The recognition ratio for chemical substances, which cause acute poisoning, is 0.97 with 98% recognition probability.

The user is given the opportunity:

- To conduct a search of the substance, which caused the poisoning, by clinical manifestations of the disease.
- To get reference information, which characterizes poisoning with the chemicals, included in the database.

NEUROTOPIC is a software program, which determines the most afflicted exposed area in the nervous sustem.

NEUROTOPIC was Structured in keeping With the principle of expert systeme

NEUROTOPIC is oriented to and integrated with a computerized anatomy atlas of the nervous system, which was created *by the same group of authors. The atlas contains written descriptions and graphic demonstrations to explain the poisoning symptoms and nervous system exposure features, which are dealt with in the software program.*

The user is also given the opportunity to:

- Define by clinical features of the disease the mainly afflicted area of the exposed nervous system;
- Get reference information, which is characteristic of the given exposed area of the nervous system;
- View descriptive and graphic explanations for the symptoms and features of exposure.

Simple and handy in u
the KAIF system enat
the doctors and stude
to operate it successfi
without special trainin

DEFIT and NEUROTOPIC software programs can be used both within the integrated KAIF system and separately. DEFIT software program is designed for toxicological centers and agencies, which deal in criminology issues. NEUROTOPIC software program will assist medical doctors and students.

KAIF system was developed by the team of the South Center for Medical and Sanitary Assistance under Chemical Emergencies at the Institute of Hygiene, Toxicology and Occupational Pathology headed by Dr. Boris N. Filatov.

South Center for Medical and Sanitary Assistance under Chemical Emergencies develops:

- Medical application computer technologies to be used in emergency situations, caused by exposure to chemical substances (decision making support systems, Chemical registers);
- Pollutant release and transfer registers;
- Health risk assessment from exposure of chemicals.

The Center has had experience of collaboration with the Harvard International Development Institute, Lawrence Livermore National Laboratory (USA) and UNEP Chemical (headquartered in Switzerland).

The Institute of Hygiene, Toxicology and Occupational Pathology is engaged in a wide spectrum of medical and environmental research, connected with super toxic substances (dioxins, chemical weapons, herbal toxins, etc.).

Contact address:
Dr. Boris Filatov,
South Center of medical Assistance
Under Chemical Emergencies
12 Zemlyachky Str., Volgograd
400048 Russia

Tel. (8442) 395359
Fax (8442) 727876
E-mail: ucmp@sprint-v.com.ru

PERCHLOROMETHYL MERCAPTAN

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3PP

TomenAgro

TOMEN AGRO, Inc.
100 First Street, Suite 1700
San Francisco, CA 94105
(415) 536-3480 FAX: (415) 284-9883

May 30, 2001

00312
C-003

Attachment 16

OPPT Document Control Office
Office of Pollution Prevention and Toxics
United States Environmental Protection Agency
East Tower Rm. G-099; Waterside Mall
401 M St., SW
Washington, DC 20024

Tel. 202-260-7093

RE: Docket Control # OPPTS-00312 (Perchloromethyl Mercaptan Proposed AEGLs)

Dear Sir/Madam:

The U.S. Environmental Protection Agency Office of Pollution Prevention and Toxics (OPPTS) has requested comments on a public draft issued in December 2000 for Proposed Acute Exposure Guideline Levels (AEGLs) on Perchloromethyl Mercaptan (CAS Reg. No. 594-42-3). The Agency sought comments on the methodology used to derive the proposed AEGLs as well as the toxicology/exposure studies that were selected as the basis for establishing AEGL-1, AEGL-2 and AEGL-3 values.

This provides the comments of Tomen Agro, Inc. on the establishment of the proposed AEGLs for perchloromethyl mercaptan (PMM).

Tomen Agro, Inc. is an agricultural chemical company with headquarters in San Francisco, California. We maintain registrations for pesticides in the United States and over 100 other countries throughout the world. Tomen Agro, Inc. uses PMM as an intermediate in the synthesis of the fungicide captan at a manufacturing facility in Perry, Ohio. Therefore it is important to our company that any exposure guidelines that are set for PMM be protective, practical, and scientifically valid.

Tomen Agro, Inc. offers the following comments:

1. **The subchronic studies that were used to establish the proposed AEGLs for PMM are not appropriate for setting acute exposure endpoints.**

    - For example, the 10- and 30-minute proposed AEGL-1 and AEGL-2 values are based upon the NOEL from a subchronic (duration $\geq$ 70 days) study. To derive these proposed AEGLs two extrapolations were required:

Contain NO CB

a) a 6 hr/day actual exposure was assumed to be representative of a single daily 10- or 30-minute exposure, and
b) a 70 day repeated exposure was assumed to be representative of a single daily exposure.

Using the results of a subchronic study that is designed to assess the effects of repeated daily exposures as a basis to set acute threshold exposure limits for 10 or 30 minutes is an inappropriate use of the data. The AEGLs that are being proposed for PMM are not based upon good risk assessment practices, are not practical, and misrepresent the acute inhalation risk to PMM.

- It is recommended that interested parties should be given the opportunity and reasonable time to develop and/or submit any new data that are appropriate to establish each proposed AEGL. Doing so will open up the opportunity for each PMM AEGL to be established using data from studies that are appropriately designed to assess short-term exposure.

2. **The "Combined Uncertainty Factor" (UF) used to establish the AEGL-1 for PMM should be "9" (Based upon a 3X UF for both intraspecies and interspecies variability) and not "10" as indicated in Appendix 1.**

3. **The proposed 8-hr AEGLs for PMM are overly conservative when compared to 8-hr acceptable exposure levels set by other authoritative organizations.**

   - Table 8 provides a comparative listing of the "Extant Standards and Guidelines for PMM" from several authoritative organizations including the proposed AEGLs from OPPTS. Where data are available for comparison, the acceptable PMM exposure levels indicated by the other organizations are clearly much higher that what is being proposed as an AEGL. For example, the 8-hr proposed AEGL-1 (0.006 ppm) is over 15-times more protective than the 0.1 ppm time-weighted-averages (TWA) that any of the other agencies (both domestic and foreign) have established as being sufficiently protective. This discrepancy suggests that the model and assumptions used by OPPTS to establish the proposed AEGLs are overly protective compared to the scientific evaluations of other credible organizations.

4. **The need to establish an AEGL for PMM is not clear.**

   - Acute exposure standards have already been set for PMM by several credible organizations that are widely recognized for their expertise in the area of worker protection (e.g., NIOSH, OSHA, ACGIH, etc.). It is questionable if establishing AEGLs for PMM will provide any benefit for protecting workers knowing that the NIOSH, OSHA, ACGIH, etc. time-

weighted-averages that are already in place have proven to be highly effective based upon the absence of any reported adverse acute exposure events to PMM.

5. **Section B of the Notice ("Characterization of the AEGLs) is misleading as to the ability of certain individuals to detect chemicals relative to the AEGLs.**

   - For accuracy, it is suggested that Section B should be modified to read, "it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described **starting** at concentrations **above or** below the corresponding AEGL level."

   - As currently written, the Notice incorrectly suggests that the general population contains only people who might be able to detect a chemical starting below its proposed AEGL. The concept of "Biological Variability", whereby a response is typically clustered around a midpoint (median), would suggest that an equal percent of the population would first be able to detect a chemical starting above its proposed AEGL. OPPTS should modify future correspondence on this subject to reflect this change.

Thank you for your consideration of these comments.

Sincerely,

Scott A. Mobley, Ph.D.
Sr. Toxicologist
Tomen Agro, Inc.

00312

C-01

Dawn Baeske <BAESKEDA@state.mi.us> on 06/01/2001 10:27:44 AM

To: NCIC OPPT/DC/USEPA/US@EPA
cc: Mary Lee Hultin <HULTINM@state.mi.us>

Attachment 17

Subject: Comments to Docket Control Numbers OPPTS-00312

Attached are our comments for the subject Docket number - in ASCI II format.

If you have any questions, please feel free to contact:

Mary Lee Hultin
Michigan Department of Environmental Quality
Air Quality Division
517-373-9845
hultinm@state.mi.us

Thank you,
Dawn Baeske
Department of Environmental Quality
Air Quality Division
517-373-7063
baeskeda@state.mi.us

ProposedAEGLCommentsMay2001.txt

May 31, 2001

Document Control Office (7407)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Document Control Office:

SUBJECT: OPPTS-00312

The following comments are being offered pursuant to the Federal Register Notice issued May 2, 2001, regarding Proposed Acute Exposure Guidance Levels (AEGL).

1. Comments on the derivation of AEGLs for acrylic acid:

The derivations of the AEGL-1 values appear to be supported with the background literature. The presumption that an interspecies uncertainty factor of 1 is warranted due to the "higher acrylic acid concentration deposited on the olfactory epitehelium of rodents compared to humans" does not seem sufficiently supported. The theories summarized from the Frederick, et al, 1998 paper, and used as support for the lowered uncertainty factor, are interesting. However, their suitability for use in risk assessment is questionable. Has the model they developed been tested and/or validated by any other researchers?

In addition, the justification for using an intraspecies uncertainty factor of 3 due to the presumption of "limited interindividual variability for local effects on the respiratory tract" does not contain a supportive reference. In fact, the data cited from Renshaw, 1988, includes reports for eye irritation ranging from 0.3-23 ppm, a range spanning approximately an order of magnitude. This report (to AIHA) is presumed to include occupationally exposed individuals, a group with considerably less heterogeneity than the general population. Since the Preface to the report (p. iii) states, "recommended exposure levels are applicable to the general population including infants and children," this degree of reduction in the intraspecies uncertainty factor does not seem appropriate.

Derivations of the AEGL-2 values: Use of the data from the Miller, 1981, subchronic study seems to be a good choice as this was also the key study used by U.S. Environmental Protection Agency (EPA) in the derivation of the RfC for this compound. As in the development of the AEGL-1 values, reduction of the interspecies uncertainty factor based on the Frederick study is questioned. For both the AEGL-2 and AEGL-3 values, reduction of the interspecies UF's based on the rationale of, "limited interindividual variability for local effects," does not seem appropriate for the reasons given above under the discussion of AEGL-1 uncertainty factors.

More detail in Appendix B on the derivation of the time-scaling factor and how ten Berge, et al., used the data in their model would provide a better template for providing comments.

One editorial note: the symbols in the key on page 20, depicting Figure 1, do not match the symbols in the graph. Therefore, it is not possible to determine precisely what the graph is intended to represent.

2. Comments on the derivation of AEGLs for tetrachloroethylene:

Obviously, use of human studies in the development of AEGL values is preferred. However, the

descriptions of the exposure estimates in the Rowe and Carpenter studies (used in derivation of the AEGL-1, and given as support for the other values) raise a question as to the accuracy/precision of the measured values. Perhaps an uncertainty factor for adequacy of database should be applied due to this fact? In the derivation of the AEGL-2 values, a reduction in the interspecies uncertainty factor is performed, reportedly due to the fact that rodents and humans experience similar effects when exposed to CNS depressants. Although this may seem to be a reasonable argument for the pharmacodynamics, the pharmacokinetics may be different between species. The interspecies and intraspecies uncertainty factors generally take both aspects into account (Renwick, A.G. 1999. Subdivision of uncertainty factors to allow for toxicokinetics and toxicodynamics. HERA, v. 5(5):1035-1050). Without supportive data, the reduct

The summary states that no developmental anomalies were found in the studies reviewed. However, the Tepe (1980) and Nelson (1980) studies describe some adverse effects in the offspring.

The positive carcinogenicity data is not noted in the descriptions of AEGL derivations. Is the increased cancer risk not considered in derivations of AEGLs?

3. Comments on the derivation of AEGLs for Allyl Alcohol (107-18-6):

The overall approach taken by the NAC/AEGL Committee in deriving the AEGLs for allyl alcohol was based on the AEGL-1's odor threshold of 1.8 ppm for all time values. This action limited the use of uncertainty factors for the AEGL-2 and -3 values. According to the Committee, use of traditional uncertainty factors, i.e., 3 to 10-fold interspecies and intraspecies, would result in inconsistent values compared with the AEGL-1 value. However, the use of uncertainty factors for an AEGL should not be dependent on constraints from other AEGL values, but should independently reflect the health and safety concerns of a particular AEGL. It appears that a combined uncertainty factor of 30 would have been used (which is the traditional method) had it not interfered with the preceding AEGL.

Another discussion point is the NAC/AEGL Committee's proposed AEGL-1 value of 1.8 ppm for all time frames. It is hoped that the committee reviewed all current relevant documentation when establishing these values. During the course of this review, it was found that The American Council of Governmental Industrial Hygienists (ACGIH) has a threshold limit value (TLV) of 0.5 ppm for allyl alcohol. This value was originally 2 ppm, but in 1998 the new value of 0.5 ppm was published under Notice of Intended Changes in their Threshold Limit Values guidebook. According to their by-laws, "if, after one year, no evidence comes to light that questions the appropriateness of the values herein, the values will be reconsidered for the "adopted" list." In 1999, the ACGIH adopted this value. A request was sent to the ACGIH for supporting documentation of this value, but this information has not yet been received to send along with this review. We urge the NAC/AEGL Committee to investigate this issue, since there is n

4. Comments on the derivation of AEGLs for Phenol (108-95-2):

The NAC/AEGL Committee selected key studies that seem to appropriately support the derivation for each of the AEGL values. But, the actual derivations didn't follow the conventional use of uncertainty factors. Typically, when using conventional uncertainty factor methodology [U.S. EPA's Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPA/600/8-90/066F; October 1994; Table 4-8.)] there can be a three-fold uncertainty factor for inter-specie extrapolation from valid results of long-term studies on experimental animals. This is in stark contrast to the rationale used for the AEGL-2, that an inter-specie uncertainty factor of one is acceptable from a two-week inhalation study (CMA). Although the other key study for the AEGL-2 produced similar results using more conventional uncertainty factors, it seems inappropriate to

extrapolate result. :m a two-week study, and use an uncertainty factor that is less than what would be used for a lo

5. Com .nts on the derivation of the proposed AEGL values for methanol (CAS 67-56-1):

The AEGL suppor ocuments explain in sufficient detail the methods used to obtain the AEGL values for methanol. The p :osed AEGL values and methodology used seem appropriate.

6. Comments on :e derivation of the proposed AEGL values for tetranitromethane (CAS # 509-14-8):

The AEGL suppo documents explain in sufficient detail the methods used to obtain the AEGL values for tetranitromethan e. The proposed AEGL values and methodology used seem appropriate. One comment on the tetranitro ethane support document involves Appendix B, which evaluates the calculation of cancer risk to acute exposure. Our office has found that a higher cancer potency value can be obtained using the male mice lung adenoma and carcinoma incidence rather than the female mice values as was used in the support document. Use of this higher potency factor would result in a slightly lower exposure to a very potent carcinogen. There is some question, however, regarding the appropriateness of trying to evaluate the lifetime cancer risk from an acute exposure.

7. Comments on the derivation of the AEGL values for Toluene (108-88-3):

Overall, the derivation of the AEGLs for Toluene seemed well reasoned. However, the 10-minute AEGL-1 of 260 ppm and the 30-minute AEGL-2 of 270 may be disproportionately close, but this could simply be reflective of a high threshold for irritation.

8. Comments on the derivation of the AEGL values for Furan (110-00-9):

A NOAEL was not identified in the only quantitative toxicology study by Terrill et al., (1989). This uncertainty was not specifically accounted for in the AEGL-2. A three-fold increase in the uncertainty factor for AEGL-2 is suggested based on LOAEL to NOAEL conversion. Concerning AEGL-3, metabolism to reactive metabolite cis-2-butene-1,4-dial may be altered at higher exposure levels, shorter time intervals, and severity of effect (i.e. lethality). A three-fold increase in the total uncertainty factor for AEGL-3 is suggested based on incomplete acute pharmacokinetic information for this endpoint. This could be tacked on to the modifying factor of three for a total modifying factor of 10. For AEGL-2 and -3 the total UF would be 300. Alternatively, an increase in the intraspecies UF from 3 to 10 could be justified based on uncertainty of metabolism. The good use of the concentration-time equation exponent n for shorter time intervals may have been part of the reasoning to keep total UF at 100, but thi

If you have any questions on the aforementioned comments, please do not hesitate to contact me. Thank you for the opportunity to provide comment on these important values.

Sincerely,

Mary Lee Hultin

Air Quality Division
517-373-9845

MLH:DB
cc: Ms. Catherine Simon, DEQ

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C-007

48512

2PP

John Morawetz <JMorawetz@ICWUC.org> on 06/01/2001 03:25:23 PM

To: NCIC OPPT/DC/USEPA/US@EPA
cc: Roger Garrett/DC/USEPA/US@EPA, Po-Yung Lu <lpy@ornl.gov>, George Rusch <george.rusch@alliedsignal.com>, Paul Tobin/DC/USEPA/US@EPA

Subject: Docket OPPTS-00312 Tetrachloroethylene

Attachment 18

Docket OPPTS-00312

Enclosed are my comments on the AEGL proposed values for tetrachloroethylene.

John S. Morawetz

(513)621-8882

CFR Tetrachloroethylene txt.doc

48512

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460

June 1, 2001

Docket control # OPPTS-00312: Tetrachloroethylene AEGL-2 value

I would like to raise a concern regarding the AEGL-2 value recommended by the AEGL Committee for Tetrachloroethylene. In particular, the Rowe study has indications that deserve greater weight in setting our AEGL-2 values.

As mentioned in the full TSD, Rowe found that at 600 ppm for 10 minutes "motor coordination required great effort". The Rowe article goes much further for higher exposures. At 1,060 ppm, three subjects "withstood the effects of the vapors for one minute before hurriedly leaving the room" while "a fourth individual tolerated the exposure for two minutes; although considerable dizziness was experienced, recovery was quite rapid". These observations are strongly supported by a statement found in the Stewart, 1961 study:

> "Vapor exposures to this compound should ***never (italics in original)*** exceed 200 ppm because of the rapid onset of lightheadedness and hence the increased risk of accidental injury resulting therefrom"

I request that the Committee reconsider and lower the current recommended AEGL-2 levels. An alternative proposal would be to start with the 600 ppm for 10 minutes and use an uncertainty factor of 3 for human variability.

John S. Morawetz

c: Frank D. Martino
Secretary Treasurer's Office
Eric Bray
Michael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Rodger Garrett, EPA

00312 48375
C-004

22pp

"Monty L. Herr" <herr2@llnl.gov> on 05/31/2001 06:19:24 PM

Attachment 19

To: NCIC OPPT/DC/USEPA/US@EPA
cc: Paul Tobin/DC/USEPA/US@EPA, monaco1@llnl.gov, epley1@llnl.gov, price16@llnl.gov, futterman1@llnl.gov

Subject: Comments: docket control number OPPTS-00312

The attached documents are comments on AEGL TSDs for G-Agents and for Agent VX. They are submitted in response to the Notice published in the Federal Register of May 2, 2001 (Volume 66, Number 85), Pages 21940-21964, and identified by docket control number OPPTS-00312.

The comments were composed in Microsoft Word and then converted to WordPerfect and Text format. Conversions didn't go as smoothly as one would hope. All three versions are attached.

Monty L. Herr, PhD, CIH Tel. (925) 422-8744
Lawrence Livermore National Laboratory Fax (925) 422-5176
L-379 e-mail: herr2@llnl.gov
P.O. Box 808
7000 East Avenue
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Combined Nerve Agent Comments.tx Combined Nerve Agent Comments.wp5.do Combined Nerve Agent Comments.do

Lawrence Livermore National Laboratory

L-379

7000 East Avenue

Livermore, CA 94551

June 1, 2001

Paul S. Tobin
Designated Federal Officer (DFO)
Office of Prevention, Pesticides and Toxic Substances (7406)
1200 Pennsylvania Ave., NW.
Washington, DC 20460

Subject: AEGL docket control number OPPTS-00312

Dear Mr. Tobin,

In the May 2, 2001, Federal Register, documents supporting Acute Exposure Guideline Levels for Nerve Agents GA, GB, GD, and GF and for Nerve Agent VX were offered for public comment. Please accept the attached comments.

Yours truly,

Monty L. Herr, PhD, CIH

Senior Scientist

Comments on AEGL docket control number OPPTS-00312 Technical Support Document for Proposed Acute Exposure Guideline Levels (AEGLs) for Nerve Agents GA, GB, GD, GF, and Technical Support Document for Proposed Acute Exposure Guideline Levels (AEGLs) for Nerve Agent VX

Prepared and Submitted by
Monty L. Herr, PhD, CIH
Lawrence Livermore National Laboratory
May 31, 2001

In the AEGL-1 and AEGL-2 derivations for GB, a total uncertainty factor of 10 was applied (derived from 10 for intraspecies variability for sensitive individuals, 1 for interspecies variability since for human data was available, and, since the database for agent GB is reasonably complete, no modifying factor). The AEGLs for the other G-agents are then derived from these GB AEGLs based on relative potencies. By doing this, there is an implicit assumption that the uncertainty factors for the other G-agents are the same as those for GB. Since the databases for the other G-agents are nowhere near as complete as for GB (including the databases used to deduce relative potency), and the data for GF are practically nonexistent, this assumption is invalid. The application of this approach is particularly inconsistent when the relative potency process based on GB is used for deriving the AEGLs in the VX TSD. In that case, a modifying factor of 3 was applied, the rationale being that for VX the data set was incomplete. The VX data set, however, is much more complete than that for GF, and not much inferior to that of the other G-agents excepting GB.

In the G-Agent TSD, Executive Summary, Page vii-viii, and Section 6.3, Page 57, second paragraph, there is a statement, "Selection of this effect [SFEMG changes] as a *protective definition* [emphasis added] of an AEGL-2 level is considered appropriate given the steep dose-response toxicity curve of nerve agents." Then on Page viii, third paragraph, there is the statement, "To accommodate known variation in human cholinesterase activity that may make some individuals susceptible to the effects of cholinesterase inhibitors such as nerve agents, a factor of 10 was applied for intraspecies variability (protection of susceptible populations)." Similarly, in Section 6.3, Page 58, fourth paragraph, there is a clause that states, "an intraspecies uncertainty factor of 10 for protection of possible sensitive individuals." Selection of a protective definition suggests that an intraspecies uncertainty factor smaller than 10 should be used.

In the G-Agent TSD, Executive Summary, Page vii-viii, the statement, "Selection of this effect as a protective definition of an AEGL-2 level is considered appropriate given the *steep dose-response toxicity curve of nerve agents*." While this statement on *steep dose-response toxicity curve of nerve agents* is reasonable, it should be discussed and supported with references and data.

There are additional sources of relevant data that have not been appropriately considered. In the G-Agent TSD, some reference is made to work performed by the Defence Research

Establishment, Suffield, Ralston, Alberta, Canada. Two papers are cited:

Yee, E., Armour, J. and R. Bide. 1999. An approach to obtain estimates of human toxicity. Part II: A three dimensional probit based, nonlinear dose response model for calculation of the mortality-concentration-time response surface. Presented to the NATO Challenge Subgroup, 12-14 May, 1999, San Antonio, Tx, and

Bide, R., Armour, J. and E. Yee. 1999. An approach to obtain estimates of human toxicity. Part III: A reasonable, defendable procedure to obtain human inhalation toxicity estimates (LCt_{05}, LCt_{50} and LCt_{95}) directly from animal toxicity data. Presented to the NATO Challenge Subgroup, 12-14 May, 1999, San Antonio, TX.

There are, however, considerably more data available from that laboratory. The Canadian researchers appear quite willing to share their information. Two draft papers from them contain significant new data on GB toxicity.

The draft papers cite several references to GB inhalation toxicity that were not considered in the GB TSD. The GB toxicity analysis is incomplete without consideration of the data in these references.

Ainsworth, M. (1954). The effect of dosage rate on the inhalation toxicity of GB to rabbits. (CBDE TP 423). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED.

Barrett, H.M. (1951). Studies on the LCt_{50} of nerve gas vapour in the rat and mouse. (Porton TP 2765). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED.

Cresthull, P., Graf, C.H. and Oberst, F.W. (1953). LCt_{50} of GB vapour by inhalation for mice, rats and pigeons exposed for 20 seconds. (MLRR 190). U.S. Army Chemical Corps Medical Laboratory, APG., MD. UNCLASSIFIED

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Dixon, R.L. and Koon, W.S. (1949). LCt_{50} for the mouse of equal parts of GB and chlorobenzene vapours. (MDR 219). U.S. Army Chemical Corps Medical Laboratory, APG. MD. UNCLASSIFIED

Fish, H.J. (1949). The performance of bombs charged GA, GB and fumaryl chloride when burst in a chamber. (SES-162). Suffield Experimental Station. UNCLASSIFIED?LIMITED (Rat)

Koon, W.S., Crook, J.W., Graf, C.H., Christenson, M.K and Oberst, F.W. (1960). The relationship of the LD_{50} and RBC-ChE_{50} in guinea pigs exposed to GB by the inhalation and intravenous routes. (CWLR 2342). U.S.Army Chemical Warfare Laboratories, APG, MD. UNCLASSIFIED

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Muir and Callaway, S. (1948). The toxicity of G compounds, Part I, The toxicity to rats of vaporized GA, GB, GD and GE. (PTP 81). Chemical Biological Defence Establishment Porton Down. UNCLASSIFIED

Muir, A. and Callaway, S. (1948). The toxicity to mice of vaporised GB, GD, and GE. (Ptn./6403/4993/48). Chemical Biological Defence Establishment Porton Down. UNCLASSIFIED.

Muir, A., Callaway, S. and Cullumbine, H. (1952). Studies in the therapy of G-poisoning. Part I. (Porton TP 300). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED. (Monkey)

Parker, J.M. and McPhail, M.K. (1953). Influence of excitement, Nembutal and Benzedrine on the toxicity of GB to the rat and hamster. (DRES TP 41), Defence Research Establishment Suffield. DECLASSIFIED.

Punte, C.L., Koon, W.S. Owens, E.J. and Cresthull, P. (1954). Comparative therapeutic effectiveness of atropine administered by inhalation and intramuscular injection in dogs exposed to GB vapor. (CMLRE-ML-52: Medical Laboratories Report 270). U.S. Army Chemical Warfare Laboratories, APG, MD. UNCLASSIFIED.

Rotariu, G., Byerrum, R., Blivaiss, B. and VanHoesen, D. (1945). Toxicity of captured C.W. Agents and related compounds. In *Informal monthly report Toxicity and Irritancy of Chemical Agents Report NS 5, August.* The University of Chicago Toxicity Laboratory, DECLASSIFIED. (Guinea Pig, Mouse, Rat, Rabbit, Cat, Dog, Monkey)

Silver, S.D., Williams, W.A. and Bray, E. (1950). Effect of atropine on rabbits gassed with GB. (CMLEM 52; Medical Division Report 21). U.S. Army Chemical Corps, Medical Division, APG. MD. UNCLASSIFIED.

Smith, D.F.G. (1954). The field treatment and care of war dogs poisoned by G agents. (Porton Technical Paper # 422). Chemical Defence Experimental Establishment, Porton Down, Wilts. UK. DECLASSIFIED.
Inhalation LCT_{50} (Mouse) 430 mg min/m^3 for 20 min.

Thomson, S. (1999). Low level inhalation exposure studies at SBCCOM. US report in *Minutes of the First Meeting of TP-12; Chemical Toxicology.* Held at DRES 27-29 September 1999. (Rat)

Trumit, J.H., Esposito, P.D., Bales, P.D. and Horowitz, P. (1953). Comparative study of GB inhalation toxicity in mice, rats, guinea pigs, cats, dogs and monkeys with exposure times between one second and several minutes. (MLRR 205). U.S. Army Chemical Corps Medical Laboratory, APG., MD. UNCLASSIFIED.

One of the draft documents provides the following toxicity data:

Inhalation LCT_{50} (Mouse) 430 mg min/m^3 for 20 min.

Inhalation LCT_{50} (Mouse) 538 mg min/m^3 for 60 min.

Inhalation LCT_{50} (Mouse) 899 mg min/m^3 for 180 min.

C. Inhalation LCT_{50} (Mouse) 1209 mg min/m^3 for 360 min.

Inhalation LCT_{50} (Mouse) 2214 mg min/m^3 for 720 min.

The document concludes that there is a threshold Inhalation LC_{50} near 3 mg/m^3 for multi-hour exposures. After considerable data analysis, the second of these documents concludes that the value of n (in $C^nT = k$) is 1.36 for animals and 1.38 for humans (in contrast to the value of 2 used in the G-Agents TSD). The document estimates LCt_{50} values of 30 (2 min) and 47 (10 min) mg.min/m^3 for man which are in good agreement with the estimate of 35 mg.min/m^3 for a 2 - 10 min exposure provided by Reutter and Wade.

Page 10, top paragraph contains the following comment, "It should be noted that untreated controls exhibited a pupil diameter decrease of $ 0.33 mm. Johns (1952) attributes this difference to observer bias and points out that there is still a relative difference between the control group and the exposure groups." While this observation does not appear to influence the conclusions of this TSD or the Johns report, it seems reasonable that the miotic effect in the controls has an alternative explanation. Controls were randomly placed in the observation chamber interspersed with experimental subjects. Controls may be been exposed to GB that off-gassed from the subjects. The concentration would have been low and would have given rise to a small effect. This explanation seems at least as plausible as attributing the effect in controls to observer bias.

In the VX TSD, the following pertinent reference from the Canadian laboratory should be reviewed and cited for its experimental studies on animal toxicity and extrapolation to humans: Bide, R., and Risk, D., 2000. Inhalation Toxicity of Aerosolized Nerve Agents, 1. VX Revisited. Technical Report DRES TR 2000- 063, Defence Research Establishment Suffield (Alberta), Canada.

This reference provides the following data:

Inhalation LCT_{50} (Mouse) 72.1 mg min/m^3

Inhalation LCT_{50} (Rat) 41.9 mg min/m^3
Inhalation LCT_{50} (Guinea Pig) 36.1 mg min/m^3

These authors note that their data demonstrate lower toxicity than earlier studies and provide convincing discussion that other inhalation studies have been whole body exposures and that the reported LCT_{50}s have contained a significant contribution from oral doses derived from grooming behavior of the rodents. This observation that whole body experiments provide significant non-inhalation contributions had been noted in an earlier report, Carroll, N.C., Hoskin, F.C.G., McPhail, M.K., and Myers, D.K., 1957, Vapour Toxicity of VE and VX to Female Mice, Suffield Technical Paper No. 121, Suffield Experimental Station, Ralston, Alberta, Canada.

In the VX TSD, Page 18, Section 4.1, First paragraph, contains the sentence, " Specific information on the metabolism of VX in humans or animals was not found in the available literature." The following pertinent references should be reviewed and cited for its experimental studies on animals:

Benschop, H.P., 1999, Toxicokinetics of O-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(") - VX] in Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways. Annual Report Cooperative Agreement DAMD17-97-2-7001, TNO Prins Maurits Laboratory, Rijswijk, The Netherlands, and

Benschop, H.P., van der Schans, M.J., and Langenberg, J.P., 2000, Toxicokinetics of O-Ethyl S-(2- Diisopropylaminoethyl) Methylphosphonothioate [(") - VX] in Rats, Hairless Guinea Pigs and Marmosets - Identifications of Metabolic Pathways. Final Report Cooperative Agreement DAMD17-97-2-7001, TNO Prins Maurits Laboratory, Rijswijk, The Netherlands.

These references provide the following data:
Intravenous LD_{50} (Hairless Guinea Pig) 28.1 ug/kg
Percutaneous LD_{50} (Hairless Guinea Pig) 125 ug/kg

In the G Agents Technical Support Document (TSD), Executive Summary, Page viii- ix, top, the statement is made, "This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Mioduszewski et al (1998)," referring to

Mioduszewski, R.J., Reutter, S.H., Thomson, S.A., Miller, L.L., and Olajos, E.J. 1998. Evaluation of airborne exposure limits for G-agents: Occupational and general population exposure criteria. ERDEC-TR-489. U.S. Department of the Army, Edgewood Research, Development and Engineering Center, U.S. Army Chemical and Biological Defense Command, Aberdeen Proving Ground, MD.

The parallel statement in the VX TSD, Executive Summary, top of Page vi, is, " This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Reutter et al. (2000)," referring to

Reutter, S.A., Mioduszewski, R.J., Thomson, S.A. 2000. Evaluation of airborne exposure limits for VX: Worker and general population exposure criteria. ECBC-TR-074. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD.

These statements should be reconciled.

In the G-Agent TSD, Executive Summary, Page vi, Paragraph 3, and Page 3, bottom paragraph, the statement, "GB is considered largely a vapor hazard, while GD is considered mainly a vapor hazard" needs clarification.

Comments on AEGL docket control number OPPTS-00312
1. Technical Support Document for Proposed Acute Exposure Guideline Levels (AEGLs) for Nerve Agents GA, GB, GD, GF, and
2. Technical Support Document for Proposed Acute Exposure Guideline Levels (AEGLs) for Nerve Agent VX

Prepared and Submitted by
Monty L. Herr, PhD, CIH
Lawrence Livermore National Laboratory
May 31, 2001

1. In the AEGL-1 and AEGL-2 derivations for GB, a total uncertainty factor of 10 was applied (derived from 10 for intraspecies variability for sensitive individuals, 1 for interspecies variability since for human data was available, and, since the database for agent GB is reasonably complete, no modifying factor). The AEGLs for the other G-agents are then derived from these GB AEGLs based on relative potencies. By doing this, there is an implicit assumption that the uncertainty factors for the other G-agents are the same as those for GB. Since the databases for the other G-agents are nowhere near as complete as for GB (including the databases used to deduce relative potency), and the data for GF are practically nonexistent, this assumption is invalid. The application of this approach is particularly inconsistent when the relative potency process based on GB is used for deriving the AEGLs in the VX TSD. In that case, a modifying factor of 3 was applied, the rationale being that for VX the data set was incomplete. The VX data set, however, is much more complete than that for GF, and not much inferior to that of the other G-agents excepting GB.

RESPONSE TO COMMENT 1: All nerve agents possess the same, well-defined mechanism of action, i.e., cholinesterase inhibition; knowledge of this fact reduces overall uncertainty in the data. Therefore, effects on target organs are expected to be similar, but differing in magnitude. As a consequence, potential variability in human response is considered to be captured by application of the maximal estimate of 10 for an intraspecies UF. The database for G-agents as a group was considered complete as a consequence of

- **Experimental data availability for multiple species, including human (for non-lethal effects)**
- **Documented non-lethal and lethal endpoints, which exhibit exposure-response data**
- **Known mechanism of toxicity, with all observed endpoints representing a response continuum to anticholinesterase exposure**
- **No uncertainties regarding reproductive and developmental effects, or carcinogenicity**

As a means of addressing variability in target organ response and making use of the experimental data available, relative potencies applied in the estimation of AEGL

values for GA, GD and GF, relative to GB, were established according to endpoint of concern. Thus, for AEGL-1 and AEGL-2 effects, GA and GB are considered equipotent and GD/GF are each considered more potent than GB by a factor of 2.0. For AEGL-3 effects, GB is considered equipotent to GD and GF, while GA is considered less potent than GB by a factor of 2.

The NAC recommended that an additional, modifying factor of 3 be applied to the AEGL estimates developed for agent VX because they judged the database for VX to be much less complete than the composite database for all the G-agents.

Consistency is thus maintained.

2. In the G-Agent TSD, Executive Summary, Page vii-viii, and Section 6.3, Page 57, second paragraph, there is a statement, "Selection of this effect [SFEMG changes] as a *protective definition* [emphasis added] of an AEGL-2 level is considered appropriate given the steep dose-response toxicity curve of nerve agents." Then on Page viii, third paragraph, there is the statement, "To accommodate known variation in human cholinesterase activity that may make some individuals susceptible to the effects of cholinesterase inhibitors such as nerve agents, a factor of 10 was applied for intraspecies variability (protection of susceptible populations)." Similarly, in Section 6.3, Page 58, fourth paragraph, there is a clause that states, "an intraspecies uncertainty factor of 10 for protection of possible sensitive individuals." Selection of a protective definition suggests that an intraspecies uncertainty factor smaller than 10 should be used.

RESPONSE TO COMMENT 2: The selection of appropriate intraspecies UF was discussed at length by the NAC, and the option of a lower value of 3 was considered. Nevertheless, NAC rejected this option in favor of an intraspecies UF value of 10, considered to be the more protective assumption by the NAC majority.

3. In the G-Agent TSD, Executive Summary, Page vii-viii, the statement, "Selection of this effect as a protective definition of an AEGL-2 level is considered appropriate given the *steep dose-response toxicity curve of nerve agents*." While this statement on *steep dose-response toxicity curve of nerve agents* is reasonable, it should be discussed and supported with references and data.

RESPONSE TO COMMENT 3: The steep dose-response of concern was illustrated to the NAC by presentation of the rat mortality curve published by Aas et al (1985) in their paper "A method for generating toxic vapors of soman: Toxicity of soman by inhalation in rats," *Toxicology and Applied Pharmacology* 80: 437-445. This curve was presented at the NAC meetings convened in both July and October 2000, and is cited at several locations in the technical support document. Use of the Aas paper as a source can be expanded in the next edition of the TSD

4. There are additional sources of relevant data that have not been appropriately considered. In the G-Agent TSD, some reference is made to work performed by the Defence Research Establishment, Suffield, Ralston, Alberta, Canada. Two papers are cited:

   - Yee, E., Armour, J. and R. Bide. 1999. An approach to obtain estimates of human toxicity. Part II: A three dimensional probit based, nonlinear dose response model for calculation of the mortality-concentration-time response surface. Presented to the NATO Challenge Subgroup, 12-14 May, 1999, San Antonio, Tx, and
   - Bide, R., Armour, J. and E. Yee. 1999. An approach to obtain estimates of human toxicity. Part III: A reasonable, defendable procedure to obtain human inhalation toxicity estimates (LCt_{05}, LCt_{50} and LCt_{95}) directly from animal toxicity data. Presented to the NATO Challenge Subgroup, 12-14 May, 1999, San Antonio, TX.

   There are, however, considerably more data available from that laboratory. The Canadian researchers appear quite willing to share their information. Two draft papers from them contain significant new data on GB toxicity.

   The draft papers cite several references to GB inhalation toxicity that were not considered in the GB TSD. The GB toxicity analysis is incomplete without consideration of the data in these references.

   - Ainsworth, M. (1954). The effect of dosage rate on the inhalation toxicity of GB to rabbits. (CBDE TP 423). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED.

   - Barrett, H.M. (1951). Studies on the LCt_{50} of nerve gas vapour in the rat and mouse. (Porton TP 2765). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED.

   - Cresthull, P., Graf, C.H. and Oberst, F.W. (1953). LCt_{50} of GB vapour by inhalation for mice, rats and pigeons exposed for 20 seconds. (MLRR 190). U.S. Army Chemical Corps Medical Laboratory, APG., MD. UNCLASSIFIED

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- Muir, A., Callaway, S. and Cullumbine, H. (1952). Studies in the therapy of G-poisoning. Part I. (Porton TP 300). Chemical Biological Defence Establishment Porton Down. DECLASSIFIED. (Monkey)

- Parker, J.M. and McPhail, M.K. (1953). Influence of excitement, Nembutal and Benzedrine on the toxicity of GB to the rat and hamster. (DRES TP 41), Defence Research Establishment Suffield. DECLASSIFIED.

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- Rotariu, G., Byerrum, R., Blivaiss, B. and VanHoesen, D. (1945). Toxicity of captured C.W. Agents and related compounds. In *Informal monthly report Toxicity and Irritancy of Chemical Agents Report NS 5, August.* The University of Chicago Toxicity Laboratory, DECLASSIFIED. (Guinea Pig, Mouse, Rat, Rabbit, Cat, Dog, Monkey)

- Silver, S.D., Williams, W.A. and Bray, E. (1950). Effect of atropine on rabbits gassed with GB. (CMLEM 52; Medical Division Report 21). U.S. Army Chemical Corps, Medical Division, APG. MD. UNCLASSIFIED.

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- Trurnit, J.H., Esposito, P.D., Bales, P.D. and Horowitz, P. (1953). Comparative study of GB inhalation toxicity in mice, rats, guinea pigs, cats, dogs and monkeys with exposure times between one second and several minutes. (MLRR 205). U.S. Army Chemical Corps Medical Laboratory, APG, MD. UNCLASSIFIED.

One of the draft documents provides the following toxicity data:

- Inhalation LCT_{50} (Mouse) 430 mg min/m^3 for 20 min.
- Inhalation LCT_{50} (Mouse) 538 mg min/m^3 for 60 min.
- Inhalation LCT_{50} (Mouse) 899 mg min/m^3 for 180 min.
- Inhalation LCT_{50} (Mouse) 1209 mg min/m^3 for 360 min.
- Inhalation LCT_{50} (Mouse) 2214 mg min/m^3 for 720 min.

The document concludes that there is a threshold Inhalation LC_{50} near 3 mg/m^3 for multi-hour exposures. After considerable data analysis, the second of these documents concludes that the value of n (in $C^nT = k$) is 1.36 for animals and 1.38 for humans (in contrast to the value of 2 used in the G-Agents TSD). The document estimates LCt_{50} values of 30 (2 min) and 47 (10 min) mg.min/m^3 for man which are in good agreement with the estimate of 35 mg.min/m^3 for a 2 - 10 min exposure provided by Reutter and Wade.

RESPONSE TO COMMENT 4: Yes, we are aware of the historical database available from DRES, and have also experienced much cooperation from these investigators in our contacts with them over the past 2 years. It is a pleasure to communicate with them.

In our several communications with Richard Bide, he has been informing us of his ongoing work to incorporate the extensive animal effects data archived at Suffield (and identified by your individual citations above) to provide human estimates for nerve agent toxicity fully based on the animal toxicity data. To that end, he and his team at DRES are re-calculating the archival data to a single set of units and are defining a combined data set for each species. One of their goals is to develop values of LCt_{50}, LCt_{05} and LCt_{95} for a range of exposure times, starting first with agent GB. These historical datasets you identified are incorporated into their model

development work. In 2000, the two papers by Yee et al (1999) and Bide et al (1999) that we cited represented the most recent summary of their model development. It is our understanding that this model development is presently being converted into open literature papers, and we have asked that we be placed on the DRES distribution list. Perhaps their latest publications will be available in time for us to incorporate their most recent insights into the next edition of the TSDs.

One of the advantages of using the Mioduszewski et al (2000 a,b) studies for estimation of the "n" value is that these experimental data were collected under modern protocols of animal care and use, as well as QA/QC for experimental design, and a highly monitored system of vapor generation for the time periods of interest to the AEGL process; further the published papers of Mioduszewski et al contain the 1999 information presented by S. Thomson in the list of citations you provide. Bide and Yee freely acknowledge that a large proportion of the data available to them are for short-term exposure periods of multiple minutes, and were performed several decades ago and under different standards for experimental protocol.

5. Page 10, top paragraph contains the following comment, "It should be noted that untreated controls exhibited a pupil diameter decrease of $\geq$ 0.33 mm. Johns (1952) attributes this difference to observer bias and points out that there is still a relative difference between the control group and the exposure groups." While this observation does not appear to influence the conclusions of this TSD or the Johns report, it seems reasonable that the miotic effect in the controls has an alternative explanation. Controls were randomly placed in the observation chamber interspersed with experimental subjects. Controls may be been exposed to GB that off-gassed from the subjects. The concentration would have been low and would have given rise to a small effect. This explanation seems at least as plausible as attributing the effect in controls to observer bias.

RESPONSE TO COMMENT 5: The explanation you provide would also explain the observation, which, as you state, does not affect the conclusion. We were quoting the author, who noted the bias and presented his explanation in the report.

6. In the VX TSD, the following pertinent reference from the Canadian laboratory should be reviewed and cited for its experimental studies on animal toxicity and extrapolation to humans: Bide, R., and Risk, D., 2000. Inhalation Toxicity of Aerosolized Nerve Agents, 1. VX Revisited. Technical Report DRES TR 2000-063, Defence Research Establishment Suffield (Alberta), Canada.

   This reference provides the following data:
   Inhalation LCT_{50} (Mouse) 72.1 mg min/m^3
   Inhalation LCT_{50} (Rat) 41.9 mg min/m^3
   Inhalation LCT_{50} (Guinea Pig) 36.1 mg min/m^3

These authors note that their data demonstrate lower toxicity than earlier studies and provide convincing discussion that other inhalation studies have been whole body exposures and that the reported LCT_{50}s have contained a significant contribution from oral doses derived from grooming behavior of the rodents. This observation that whole body experiments provide significant non-inhalation contributions had been noted in an earlier report, Carroll, N.C., Hoskin, F.C.G., McPhail, M.K., and Myers, D.K., 1957, Vapour Toxicity of VE and VX to Female Mice, Suffield Technical Paper No. 121, Suffield Experimental Station, Ralston, Alberta, Canada.

RESPONSE TO COMMENT 6: Thank you for providing us with a hardcopy of this recent DRES report on aerosolized VX inhalation toxicity. At this time, the Office of the Army Surgeon General is primarily concerned with aspects of exposure to VX agent vapors, rather than aerosols. This determination is due to the greater potential for downwind transport of VX vapor, relative to VX aerosols, following an agent release event. VX aerosols may be evaluated separately by the NAC in the future, at which time the Bide and Risk (2000) Technical Report DRES TR 2000-063 you provided will be very helpful to the analysis.

We agree that whole-body exposure to aerosols would certainly result in deposition on the pelts of experimental animals and become a source of ingestion exposure via grooming behavior.

7. In the VX TSD, Page 18, Section 4.1, First paragraph, contains the sentence, "Specific information on the metabolism of VX in humans or animals was not found in the available literature." The following pertinent references should be reviewed and cited for its experimental studies on animals:

   Benschop, H.P., 1999, Toxicokinetics of O-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(±) – VX] in Hairless Guinea Pigs and Marmosets – Identification of Metabolic Pathways. Annual Report Cooperative Agreement DAMD17-97-2-7001, TNO Prins Maurits Laboratory, Rijswijk, The Netherlands, and

   Benschop, H.P., van der Schans, M.J., and Langenberg, J.P., 2000, Toxicokinetics of O-Ethyl S-(2- Diisopropylaminoethyl) Methylphosphonothioate [(±) – VX] in Rats, Hairless Guinea Pigs and Marmosets – Identifications of Metabolic Pathways. Final Report Cooperative Agreement DAMD17-97-2-7001, TNO Prins Maurits Laboratory, Rijswijk, The Netherlands.

   These references provide the following data:

   - Intravenous LD_{50} (Hairless Guinea Pig) 28.1 ug/kg

- Percutaneous LD_{50} (Hairless Guinea Pig) 125 ug/kg

RESPONSE TOP COMMENT 7: Thank you for providing us the citations to these internal reports from the TNO Lab. I will initiate a request for these and any other more recent reports on this topic and hope to add additional information on VX toxicokinetics to the next edition of the VX technical support document.

8. In the G Agents Technical Support Document (TSD), Executive Summary, Page viii-ix, top, the statement is made, "This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Mioduszewski et al (1998)," referring to

   Mioduszewski, R.J., Reutter, S.H., Thomson, S.A., Miller, L.L., and Olajos, E.J. 1998. Evaluation of airborne exposure limits for G-agents: Occupational and general population exposure criteria. ERDEC-TR-489. U.S. Department of the Army, Edgewood Research, Development and Engineering Center, U.S. Army Chemical and Biological Defense Command, Aberdeen Proving Ground, MD.

   The parallel statement in the VX TSD, Executive Summary, top of Page vi, is, "This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Reutter et al. (2000)," referring to

   Reutter, S.A., Mioduszewski, R.J., Thomson, S.A. 2000. Evaluation of airborne exposure limits for VX: Worker and general population exposure criteria. ECBC-TR-074. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD.

   These statements should be reconciled.

   RESPONSE TO COMMENT 8: Contact with the commentor indicates the concern is regarding precision of wording as to which source is the "most" recent as an example of relative potency application for comparison of nerve agent toxicity. The text wording will be clarified with text changes approved by the commentor.

9. In the G-Agent TSD, Executive Summary, Page vi, Paragraph 3, and Page 3, bottom paragraph, the statement, "GB is considered largely a vapor hazard, while GD is considered mainly a vapor hazard" needs clarification.

RESPONSE TO COMMENT 9: The use of the terms "largely" and "mainly" is military terminology (from Army Field Manual FM 3-9) indicating operational consideration of relative volatility for these two compounds. Agent GB is considered highly volatile; so much so that small droplets sprayed from an aircraft or released from an exploding shell may never reach the ground. Operationally, agent GD is considered less volatile, so it is termed "mainly" a vapor hazard. These

were not intended to be precise terms, and new wording can be added to the TSD for clarification.

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Attachment 20

Docket Control Number OPPTS-00312
Comments on the Nerve Agent VX (CAS Reg. No. 50782-69-9) Proposed Temporary Acute Exposure Guideline Levels (AEGLs). "Public Draft" Proposed Temporary 1: 10/2000
Comments by Christopher Bittner, Utah Division of Solid and Hazardous Waste, P.O. Box 144880 Salt Lake City, UT 84114-4880 Phone 801-538-6813 cbittner@deq.state.ut.us

GENERAL COMMENTS:

Comment 1: The available data does not support the use of a single relative potency value of 10 for comparing the toxicity VX to GB. For a single relative potency to be valid for all toxicological endpoints or exposure regimes (*e.g.*, exposure route, exposure duration) , the dose-response curves for GB and VX would be parallel. The available data suggests that the potency varies depending on the toxicological endpoint and exposure regime. Table 7, Relative Potency Estimates for Agents GB and VX-Experimental Data, illustrates a range of relative potencies from 1.8 to 241. Table 8, Human Toxicity Estimates for Agents GB and VX illustrates a range of relative potencies of 2.3 to 25. At the CDC meeting, Dr. Weyandt informed the panel that "... a relative potency of VX [to GB] through various means of exposure ranged from 2 to 100 with the predominant number being 10." (DHHS, 2000). The proposed AEGLs are based on different exposure durations and different toxicological endpoints. Therefore, a single relative potency value is not appropriate.

Proposed Action: The relative potency should be derived based on the experimental data that matches the exposure regime and toxicological endpoint of the AEGL. If the experimental data is inadequate, a single relative potency would be appropriate provided that the potency can be demonstrated to be protective of human health for the AEGLs.

SPECIFIC COMMENTS:

Comment 2: Executive Summary, third paragraph. The text states "Toxic effects may occur at concentrations below those of odor detection." While technically accurate, the statement is misleading because VX is odorless (USACHPPM, TG 218) and would not detectable at any concentration.

Proposed Action: Revise the statement to indicate that VX is odorless and tasteless.

Comment 3: Section 2.2.1 Acute Exposure Studies (also Table 4. Suspect Human Experimental Data for VX Vapor (table footnote) and Section 3.2 Nonlethal Toxicity). The characterization that the U.S. Surgeon General's Review Panel (DHHS, 2000) concurred with Reutter's et al. (2000) rejection of Bramwell et al. (1963) is inaccurate. The study of Bramwell et al. (1963) has serious limitations. However, at least one panel member did not concur to reject Bramwell et al. (1963). In contrast, Bittner recommended that the Airborne Exposure Limits (Reutter et al. (2000) based on Bramwell et al. (1963) be adopted (Bittner, 2000). Based on the comparisons presented in Table 8 (Human Toxicity Estimates for Agents GB and VX) of the AEGL document, the results of Bramwell et al. (1963) are consistent with the other studies.

Proposed Action: Revise all statements to indicate that the panel (DHHS, 2000) concurred that Bramwell et al. (1963) has serious limitations.

Comment 4: Section 3.3 Neurotoxicity. It is unclear if this section is a summary of Opresko et al. (1998).

Proposed Action: Include the stand-alone sentence referencing Opresko et al. (1998) with the previous paragraph.

Comment 5: Table 7, Relative Potency Estimates for Agents GB and VX-Experimental Data. Footnote notation "g" is used twice in the table and the footnotes.

Proposed Action: Renumber footnotes

Comment 6: Section 4.3 Relative Potency, Comparison of Exposure Standards. The derivation of the relative potency of 10 (4/25) is explained. The AEGLs are derived for exposure durations of 10 minutes to eight hours. The numerator (of 4/25) in calculating the relative potency of 10 relies on the slower aging of the VX-acetylcholinesterase complex resulting in a higher spontaneous regeneration of acetylcholinesterase than with GB. From the data provided, the reader cannot determine the exposure duration at which spontaneous regeneration of acetylcholinesterase would be significant. It seems unlikely that for a 10 minute exposure period for the AEGLs that spontaneous regeneration of acetyl cholinesterase would be a relevant reaction.

Proposed Action: Reconsider the appropriateness of assuming a constant relative potency for different toxicological endpoints and exposure durations. Document the basis for the numerator of 4 for calculating the relative potency.

Comment 7: Section 4.3 Relative Potency, Comparison of Exposure Standards. At least one member of the Surgeon General's Review panel (Bittner) did not support the relative potency of 10 as indicated in this section of the AEGL document.

Proposed Action: Revise the text to indicate that some members of the Surgeon General's Review panel support a relative potency of 10.

Comment 8: Section 4.3 Relative Potency, Selection of VX Potency Value for Use in Deriving AEGLs and Section 4.5.6 Critical Effect Endpoint. The USEPA (2000) weight-of-evidence approach is discussed and is identified as the source for recommending that the "first priority is given to clinical signs and physiological or behavorial effects..." The AEGL document also suggests that RBC-ChE and plasma ChE are the least desireable ("Of the six elements...the last two). In contrast, USEPA (2000) states: "Briefly, the weight of evidence approach considers all of the available data on:..." and goes on to list the six bulleted items. USEPA (2000) is not implicit or explicit that the items are in order of preference and emphasized in the response to comments that an integrated approach using all data was preferred. USEPA (2000) does not suggest a preference or priority for the different types of data and should not be the basis for

rejecting cholinesterase as the critcial endpoint.

Proposed Action: Revise the text to accurately describe the recommendations of USEPA (2000) or delete the reference to USEPA (2000).

Comment 9: Section 4.3 Relative Potency, Selection of VX Potency Value for Use in Deriving AEGLs. For estimating the relative potency of VX to GB, the concentration resulting in 90 percent pupil area decrement from Callaway and Dirnhurber (1971) was used. Callaway and Dirnhuber (1971) also measured the air concentration of VX associated with 50 percent pupil decrement (see Table 7 of the AEGL document). The relative potency of VX to GB at 50 percent pupil decrement is 33. The rationale is given that the relative potency based on 90 percent decrement is more appropriate because Callaway and Dirnhurber (1971) suggested that this endpoint was more definitive. More severe effects are often more definitive but that is not sufficient rationale. The lower effects level (*i.e.*, 50 percent reduction in pupil area) is a more appropriate than the higher effects level because a LOAEL is preferred. Even the 50 percent decrement is marginal as the LOAEL because smaller reductions in area can be reliably detected. Other investigators have recommended the 50 percent decrement. For estimating the relative potency of GA compared to GB, Mioduszewski et al (1998) relied on Reutter and Wade (1994) who used the relative potency at a 50 percent reduction in pupil area determined by Callaway and Dirnhuber (1971).

Proposed Action: In the absence of data to validate one of the relative potency estimates over the other in Callaway and Dirnhurber (1971) the more protective value (33) is appropriate. If the AEGL committee believes that there is a difference in emergency response workers between 50 and 90 pupil decrement, then perhaps a different relative potency would be appropriate for calculating the AEGL-1 and AEGL-2.

Comment 10: Section 4.4 Structure-Activity Relationships. The analysis conducted in this section concludes that the relative potency of VX to GB is considerably less than 40. However, based on the data provided, the conclusion should be that the relatively potency of VX to GB is considerably greater than 40. A racemic mixture of D- and L-isomers of GB would be less toxic than just the L-isomer. VX was tested to be 40 times more potent than L-isomer. Therefore, relative potency of VX to the racemic mixture of GB would be substantially greater than 40 (less than 400 to 800 based on 40 x 10 or 40 x 20).

Proposed Action: Review the Mager (1981) study and revise the text as necessary. Reconsider the implications to the proposed relative potency of 12.

Comment 11: Section 4.5.1 Breathing Rates and Toxicity. A dosimetric adjustment for breathing rate is not necessary or the AEGL-1 and AEGL-2 because the critical effect is miosis. A dosimetric adjustment appears to be appropriate for the AEGL-3. Does the AEGL-3 for GB (the basis for the VX AEGLs) include a dosimetric adjustment?

Proposed Action: Evaluate the need for a dosimetric adjustment for AEGL-3. Document the results of the evaluation.

Comment 12: Section 4.5.3 Intra- and Inter-Species Variability in Esterase Activity and Response to Nerve Agents. Intraspecies variation: Reduced plasma ChE is discussed as resulting in a greater sensitivity to VX. Given that VX preferentially binds to red-blood cell cholinesterase (see Section 4.1 Metabolism and Disposition of the AEGL document), would a lower plasma cholinesterase likely be relevant to VX?

Proposed Action: Evaluate the relevance of lower plasma cholinesterase and revise the text as appropriate. Also review the discussion in Interspecies variation regarding plasma cholinesterase and revise as appropriate.

Comment 13: Section 4.5.5 Concurrent Exposure Issues Multiple Exposure Through Different Exposure Pathways: The minute-concentration for mice from Koon et al. (1960) is incorrectly cited as 11.5 mg-min/m^3. The correct value is 4 mg-min/m^3.

Proposed Action: Make the correction.

Comment 14: Appendix A, Scaling. No data specific to VX is provided to support the value of n = 2 for in the equation $C^n \times t = k$ used for time scaling. The value of two is based on GB. What is the default value for n in the absence of data? Is the value of 2 protective?

Proposed Action: Evaluate the appropriateness of the n = 2 and document why this value is protective of human health in the absence of data specific to VX.

Comment 15: Appendix A, Uncertainty Factors. The factor of 10 for intraspecies is appropriate.

Comment 16: Appendix A, Modifying Factor. The proposed modifying factor of three for limitations in VX database used for all AEGLs in inadequate. As noted in the Executive Summary, "The few studies available are historical, and are considered nonverifiable due to flawed study design, poor sampling techniques, or suspect contamination of sampling and detection apparatus". Statements in the section for AEGL-3 include: "The NAC noted that an earlier report by the National Research Council (NRC, 1997) included an evaluation of the same VX toxicity data base, and had recommended at that time that additional research was needed to more fully characterize the toxicity of VX vapor.... To acknowledge the significant gaps in the data base for this nerve agent, the NAC considers the proposed AEGL values to be temporary in nature and subject to re-evaluation in 3 years." The lack of data and predicted steep dose-response curve warrant a full data base uncertainty factor of 10 to avoid under-predicting the toxic effects of VX.

Proposed Action: Whether it is called a data base uncertainty factor or a modifying factor for data base uncertainty, change the value to 10.

Comment 17: Appendix A. AEGL-3. The relative potency of 10 for the toxicity of VX compared to GB is not sufficient if 10 is the appropriate relative potency for the AEGL-1 and AEGL-2. The critical effect for the AEGL-1 and AEGL-2 is miosis. For miosis, the substantially greater dermal hazard of VX compared to GB is not likely relevant. However, for

the lethality endpoint used for the AEGL-3, the significant amount of dermal absorption of VX compared to GB (e.g., see NRC, 1997) should be accounted for in determining the relative potency for the lethality endpoint.

Proposed Action: Re-evaluate the appropriateness of the relative potency of 10 for the AEGL-3)

References.

Bittner, C. 2000 Letter to Dr. Paul Joe, CDC, Comments on Proposed Airborne Exposure Limits for the G-Chemical Agents and VX. September 21, 2000.

Bramwell, E.C.B., W.S.S. Ladell, and R.J. Shepard. 1963. *Human Exposure to VX Vapour*, PTP830

Callaway, S. and P. Dirnhuber. 1971. *Estimation of the Concentration of Nerve Agent Vapour Required to Produce Measured Degrees of Miosis in Rabbit and Human Eyes.* CDE, July. Porton Down

DHHS, 2000. Department of Health and Human Services Centers for Disease Control and Prevention. Verbatim Transcript of the Public Meeting of the Review of Safe Airborne Exposure Limits for Nerve Agents GA, GB, and VX. Atlanta, Georgia, August, 2000.

Mioduszewski, R.J., S.A. Reutter, L.L. Miller, O.J. Olajos, and S.A. Thomsom. 1998. *Evaluation of Airborne Exposure Limits for G-Agents: Worker and General Population Exposure Criteria.* April, 1998 and 2000 Addendum

NRC (Committee on Toxicology National Research Council). 1997. *Review of Acute Human-Toxicity Estimates for Selected Chemical Warfare Agents*. National Academy Press, Washington, D.C.

USACHPPM (United States Army Center for Health Promotion and Preventive Medicine) TG18. United States Army Center for Health Promotion and Preventative Medicine. *Detailed and General Facts About Chemical Agents - TG 218*

USEPA (United States Environmental Protection Agency), 2000. *The Use of Data on Cholinestesterase Inhibition for Risk Assessements of Organophorus and Carbamate Pesticides.* Office of Pesticide Programs. August 18, 2000.

Docket Control Number OPPTS-00312
Comments on the Nerve Agent VX (CAS Reg. No. 50782-69-9) Proposed Temporary Acute Exposure Guideline Levels (AEGLs). "Public Draft" Proposed Temporary 1: 10/2000
Comments by Christopher Bittner, Utah Division of Solid and Hazardous Waste, P.O. Box 144880 Salt Lake City, UT 84114-4880 Phone 801-538-6813 cbittner@deq.state.ut.us

GENERAL COMMENTS:

Comment 1: The available data does not support the use of a single relative potency value of 10 for comparing the toxicity VX to GB. For a single relative potency to be valid for all toxicological endpoints or exposure regimes (*e.g.,* exposure route, exposure duration) , the dose-response curves for GB and VX would be parallel. The available data suggests that the potency varies depending on the toxicological endpoint and exposure regime. Table 7, Relative Potency Estimates for Agents GB and VX-Experimental Data, illustrates a range of relative potencies from 1.8 to 241. Table 8, Human Toxicity Estimates for Agents GB and VX illustrates a range of relative potencies of 2.3 to 25. At the CDC meeting, Dr. Weyandt informed the panel that "... a relative potency of VX [to GB] through various means of exposure ranged from 2 to 100 with the predominant number being 10." (DHHS, 2000). The proposed AEGLs are based on different exposure durations and different toxicological endpoints. Therefore, a single relative potency value is not appropriate.

Proposed Action: The relative potency should be derived based on the experimental data that matches the exposure regime and toxicological endpoint of the AEGL. If the experimental data is inadequate, a single relative potency would be appropriate provided that the potency can be demonstrated to be protective of human health for the AEGLs.

RESPONSE TO GENERAL COMMENT 1: A relative potency value of 12 was selected by the NAC for use in all AEGL estimations for agent VX vapor effects relative to GB vapor exposures sufficient to attain the same biological endpoint. The commentor is in error by assuming a relative potency factor of 10.

For completeness, Tables 7 and 8 of the Technical Support Document summarize available information from both experimental (primary; depicted as bolded entries in TSD Tables 7 and 8) sources, and calculated estimates from mathematical models and other secondary sources. The commentor is quoting the range covered by the combined primary and secondary sources.

Experimental data take precedence in development of AEGL estimates; Section 2.3.2 of the *Standing Operating Procedures of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances* (in press by National Academy Press) clearly states "It is important to emphasize that only toxicity data obtained directly from a primary reference source is used as the basis for "key" toxicity studies from which the AEGL values are derived. Additionally, all supporting data and information important to

the derivation of an AEGL value is obtained solely from the primary references."

The range of GB/VX ratios represented by experimental results and summarized in Tables 7 and 8 is much smaller (4.2 to 33) and includes data for humans (ChE_{50} for inhalation and oral exposures), rats (subcutaneous LD_{50}), and rabbits (miosis; 50% and 90% pupil area decrement). The maximal experimental GB/VX ratio is that for 50% pupil area decrement in rabbits from the study by Callaway and Dirnhuber (1971); the range of the remaining ratios is 4.2 to 19.

The NAC determined that the well-conducted experimental study of Callaway and Dirnhuber (1971) was the best available study of toxic response comparing agents GB and VX. Further, the NAC determined that the endpoint of 90% pupil area decrement has operational significance for civilian and military emergency response, and agreed with Callaway and Dirnhuber that 90% pupil area decrement is a more definitive endpoint than 50% decrement. As a consequence, the NAC determined that the GB/VX ratio derived from Callaway and Dirnhuber (1971) data on 90% pupil area decrement in the rabbit eye was the best that could be determined at this time.

The NAC and the commentor are in agreement on the need for more and better experimental data characterizing agent VX vapor toxicity. As a consequence, the NAC has identified specific research studies whose performance would reduce uncertainties in the estimate, and declared the AEGL estimates for agent VX to be temporary and subject to re-evaluation by the NAC in 3 years. In this manner, the NAC has acknowledged existing data gaps and has encouraged collection of new data to elucidate dose response curves.

The relative potency determination currently used in developing proposed AEGL estimates for agent VX vapor is supported by existing experimental data and represents a reasonable approach that should stand until additional and well-conducted experimental data permit an alternative determination. The commentor's remarks were made without complete knowledge of the SOPs, and provide no new insight. It is recommended that no change in the relative potency factor be made at this time.

SPECIFIC COMMENTS:

Comment 2: Executive Summary, third paragraph. The text states "Toxic effects may occur at concentrations below those of odor detection." While technically accurate, the statement is misleading because VX is odorless (USACHPPM, TG 218) and would not detectable at any concentration.

Proposed Action: Revise the statement to indicate that VX is odorless and tasteless.

RESPONSE TO SPECIFIC COMMENT 2: A statement and protocol regarding odor

threshold has been a standard requirement for AEGL technical support documents over the past several years. Suggested alternate wording is "Because agent VX is considered odorless, toxic effects could occur at concentrations below those of odor detection."

Comment 3: Section 2.2.1 Acute Exposure Studies (also Table 4. Suspect Human Experimental Data for VX Vapor (table footnote) and Section 3.2 Nonlethal Toxicity). The characterization that the U.S. Surgeon General's Review Panel (DHHS, 2000) concurred with Reutter's et al. (2000) rejection of Bramwell et al. (1963) is inaccurate. The study of Bramwell et al. (1963) has serious limitations. However, at least one panel member did not concur to reject Bramwell et al. (1963). In contrast, Bittner recommended that the Airborne Exposure Limits (Reutter et al. (2000) based on Bramwell et al. (1963) be adopted (Bittner, 2000). Based on the comparisons presented in Table 8 (Human Toxicity Estimates for Agents GB and VX) of the AEGL document, the results of Bramwell et al. (1963) are consistent with the other studies.

Proposed Action: Revise all statements to indicate that the panel (DHHS, 2000) concurred that Bramwell et al. (1963) has serious limitations.

RESPONSE TO SPECIFIC COMMENT 3: One of the Agent VX AEGL TSD authors and a NAC Chemical Reviewer both attended the subject CDC public hearing mentioned by the commentor, and are familiar with the discussions that ensued. Recommended new text is as follows: "The majority of a US Surgeon General's Review Panel concurred with this appraisal of Bramwell et al. (1963) at a recent public hearing convened by CDC to examine the Reutter et al. (2000) report."

Comment 4: Section 3.3 Neurotoxicity. It is unclear if this section is a summary of Opresko et al. (1998).

Proposed Action: Include the stand-alone sentence referencing Opresko et al. (1998) with the previous paragraph.

RESPONSE TO SPECIFIC COMMENT 4: This section was not intended as a summary of the paper by Opresko et al (1998), although the topics covered in this text are certainly addressed in Opresko et al (as well as numerous other summary papers present in the literature). The reference to Opresko et al was intended to incorporate by reference a detailed and heavily documented, peer-reviewed account of nerve agent toxicity and physiology for the interested investigator.

It is recommended that the TSD text remain unaltered.

Comment 5: Table 7, Relative Potency Estimates for Agents GB and VX-Experimental Data. Footnote notation "g" is used twice in the table and the footnotes.

Proposed Action: Renumber footnotes

RESPONSE TO SPECIFIC COMMENT 5: Thank you for catching this typographical error, which will be corrected in the next edition of the technical support document.

Comment 6: Section 4.3 Relative Potency, Comparison of Exposure Standards. The derivation of the relative potency of 10 (4/25) is explained. The AEGLs are derived for exposure durations of 10 minutes to eight hours. The numerator (of 4/25) in calculating the relative potency of 10 relies on the slower aging of the VX-acetylcholinesterase complex resulting in a higher spontaneous regeneration of acetylcholinesterase than with GB. From the data provided, the reader cannot determine the exposure duration at which spontaneous regeneration of acetylcholinesterase would be significant. It seems unlikely that for a 10 minute exposure period for the AEGLs that spontaneous regeneration of acetyl cholinesterase would be a relevant reaction.

Proposed Action: Reconsider the appropriateness of assuming a constant relative potency for different toxicological endpoints and exposure durations. Document the basis for the numerator of 4 for calculating the relative potency.

RESPONSE TO SPECIFIC COMMENT 6: Please see response to General Comment 1 above for background and NAC logic in selecting a relative potency factor of 12 for agent VX.

Comment 7: Section 4.3 Relative Potency, Comparison of Exposure Standards. At least one member of the Surgeon General's Review panel (Bittner) did not support the relative potency of 10 as indicated in this section of the AEGL document.

Proposed Action: Revise the text to indicate that some members of the Surgeon General's Review panel support a relative potency of 10.

RESPONSE TO SPECIFIC COMMENT 7: One of the Agent VX AEGL TSD authors and a NAC Chemical Reviewer both attended the subject CDC public hearing mentioned by the commentor, and are familiar with the discussions that ensued. Recommended new text is as follows: "The ratio of 1/10 used by the Army in deriving exposure criteria for VX (Reutter et al., 2000) and supported by the majority of a US Surgeon General's Review Panel convened by the CDC in August 2000, was to allow for a greater margin of safety."

Comment 8: Section 4.3 Relative Potency, Selection of VX Potency Value for Use in Deriving AEGLs and Section 4.5.6 Critical Effect Endpoint. The USEPA (2000) weight-of-evidence approach is discussed and is identified as the source for recommending that the "first priority is given to clinical signs and physiological or behavorial effects..." The AEGL document also suggests that RBC-ChE and plasma ChE are the least desireable ("Of the six elements...the last two). In contrast, USEPA (2000) states: "Briefly, the weight of evidence approach considers all

of the available data on:..." and goes on to list the six bulleted items. USEPA (2000) is not implicit or explicit that the items are in order of preference and emphasized in the response to comments that an integrated approach using all data was preferred. USEPA (2000) does not suggest a preference or priority for the different types of data and should not be the basis for rejecting cholinesterase as the critcial endpoint.

Proposed Action: Revise the text to accurately describe the recommendations of USEPA (2000) or delete the reference to USEPA (2000).

RESPONSE TO SPECIFIC COMMENT 8: The *Office of Pesticide Program Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides* (USEPA 2000) clearly states that blood cholinesterase inhibition is a useful biomarker of exposure to an anticholinesterase (p. 30), but that there is no fixed percentage of (activity) change that can separate adverse from non-adverse effects (p. 37). While the *Science Policy* certainly recommends consideration of the entire dataset for any given compound, a principle conclusion of the report is that "Clinical signs/symptoms in humans and behavioral or physiological effects in humans and animals provide the most direct evidence of the potential adverse consequences of human exposure to anticholinesterase pesticides" (p. 19). There is sound toxicological and physiological logic for making this determination.

The current text of the Technical Support Document is accurate as composed in its characterization of the *Science Policy* weight-of evidence analysis.

Comment 9: Section 4.3 Relative Potency, Selection of VX Potency Value for Use in Deriving AEGLs. For estimating the relative potency of VX to GB, the concentration resulting in 90 percent pupil area decrement from Callaway and Dirnhurber (1971) was used. Callaway and Dirnhuber (1971) also measured the air concentration of VX associated with 50 percent pupil decrement (see Table 7 of the AEGL document). The relative potency of VX to GB at 50 percent pupil decrement is 33. The rationale is given that the relative potency based on 90 percent decrement is more appropriate because Callaway and Dirnhurber (1971) suggested that this endpoint was more definitive. More severe effects are often more definitive but that is not sufficient rationale. The lower effects level (*i.e.*, 50 percent reduction in pupil area) is a more appropriate than the higher effects level because a LOAEL is preferred. Even the 50 percent decrement is marginal as the LOAEL because smaller reductions in area can be reliably detected. Other investigators have recommended the 50 percent decrement. For estimating the relative potency of GA compared to GB, Mioduszewski et al (1998) relied on Reutter and Wade (1994) who used the relative potency at a 50 percent reduction in pupil area determined by Callaway and Dirnhuber (1971).

Proposed Action: In the absence of data to validate one of the relative potency estimates over the other in Callaway and Dirnhurber (1971) the more protective value (33) is appropriate. If the AEGL committee believes that there is a difference in emergency response workers between 50

and 90 pupil decrement, then perhaps a different relative potency would be appropriate for calculating the AEGL-1 and AEGL-2.

RESPONSE TO SPECIFIC COMMENT 9: Please see response to General Comment 1 above for background and NAC logic in selecting the most appropriate endpoint and a relative potency factor of 12 for agent VX.

Comment 10: Section 4.4 Structure-Activity Relationships. The analysis conducted in this section concludes that the relative potency of VX to GB is considerably less than 40. However, based on the data provided, the conclusion should be that the relatively potency of VX to GB is considerably greater than 40. A racemic mixture of D- and L-isomers of GB would be less toxic than just the L-isomer. VX was tested to be 40 times more potent than L-isomer. Therefore, relative potency of VX to the racemic mixture of GB would be substantially greater than 40 (less than 400 to 800 based on 40 x 10 or 40 x 20).

Proposed Action: Review the Mager (1981) study and revise the text as necessary. Reconsider the implications to the proposed relative potency of 12.

RESPONSE TO SPECIFIC COMMENT 10: The commentor is correct in pointing out that the isomeric composition of agent in munition storage or the field is not known. As a consequence, it is mere speculation to attempt to estimate the properties of an uncharacterized isomeric mixture in the absence of specific experimental data. For clarity, the text presenting this speculative assessment will be excised from the document.

Comment 11: Section 4.5.1 Breathing Rates and Toxicity. A dosimetric adjustment for breathing rate is not necessary or the AEGL-1 and AEGL-2 because the critical effect is miosis. A dosimetric adjustment appears to be appropriate for the AEGL-3. Does the AEGL-3 for GB (the basis for the VX AEGLs) include a dosimetric adjustment?

Proposed Action: Evaluate the need for a dosimetric adjustment for AEGL-3. Document the results of the evaluation.

RESPONSE TO SPECIFIC COMMENT 11: As is true for all AEGL determinations (primarily hazardous industrial compounds), the NAC/AEGL committee currently does not make dosimetric adjustment for attaining human-equivalent doses in the development of AEGL values. The reasoning is that, although a number of methods have been proposed by various bodies and individual investigators, there has not been sufficient validation with experimental data for determination of the most appropriate and scientifically sound approach. Until such time, the AEGL process will refrain from performing dosimetric adjustment for attaining human-equivalent doses.

This position of the NAC is documented in Section 2.4 "Dosimetry Corrections from Animal to Human Exposures," of the *Standing Operating Procedures for Developing Acute*

Exposure Guideline Levels for Hazardous Chemicals (NRC [National Research Council], 2001; *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals.* Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels. National Academy Press, Washington, DC).

As is true for AEGL-3 determinations for agent GB, the composite UF applied in the determination of an AEGL-3 for agent VX does not include any adjustment for interspecies differences in dosimetry due to species differences in breathing rates, minute volumes and body weight. For systemic poisons that are 100% absorbed, the minute volume-body weight normalization method results in a human equivalent concentration approximately 3.5 times greater than that for rats for the same endpoint (NRC, 2001). However, for high exposure levels such as those at the AEGL-3 level, absorption may be less than 100% and the estimated human equivalent exposure may be excessively high, resulting in an underestimation of the toxicity of the compound (NRC, 2001). Another possible dosimetric adjustment is one using the inhaled dose against the body weight raised to the 3/4 power (EPA, 1992). This approach is supported by the results of chronic toxicity studies, but may not be relevant for acute lethality endpoints (NRC, 2001). When applied to breathing rates, this adjustment predicts that rats would receive a dose about four times greater than humans. When this adjustment for breathing rate is combined with the adjustment for toxicity (EPA, 1992), the two cancel each other out, and the conclusion is reached that equivalent exposures result in equivalent results in both rats and humans (NRC, 2001). Use of the EPA RfC dosimetric method for systemically acting Category 2 gases (gases that are moderately water soluble and intermediate in reactivity, and would therefore be distributed throughout the respiratory tract and readily absorbed into the blood stream) results in the prediction that humans would receive a dose ranging from 6,000 to 50,000 times greater than a rodent (depending on the species) for an equivalent exposure (NRC, 2001). These numbers are not considered biologically reasonable or scientifically credible by the NRC (2001).

Given the uncertainties surrounding the issue of dosimetric adjustment across species, and the fact that no dosimetric correction would be the most conservative public health approach, the NAC/AEGL Committee decided that it would not use dosimetry corrections across species unless there were sufficient data on a specific chemical to support their use. Dosimetric adjustments for nerve agents are complicated by the fact that species response to cholinesterase inhibitors are affected to an extent by levels of endogenous enzymes that bind with the inhibitors. Some of these detoxification pathways are present in rodents but not in humans. Therefore, a dosimetric adjustment alone may be insufficient to account for interspecies differences in response to nerve agents. As a consequence, the NAC has determined that no dosimetric adjustment is required for these compounds, including agent VX.

Comment 12: Section 4.5.3 Intra- and Inter-Species Variability in Esterase Activity and Response to Nerve Agents. Intraspecies variation: Reduced plasma ChE is discussed as resulting

in a greater sensitivity to VX. Given that VX preferentially binds to red-blood cell cholinesterase (see Section 4.1 Metabolism and Disposition of the AEGL document), would a lower plasma cholinesterase likely be relevant to VX?

Proposed Action: Evaluate the relevance of lower plasma cholinesterase and revise the text as appropriate. Also review the discussion in Interspecies variation regarding plasma cholinesterase and revise as appropriate.

RESPONSE TO SPECIFIC COMMENT 12: While the biological role of plasma cholinesterase is, at present, incompletely known, it is acknowledged that plasma cholinesterase may likely serve as buffer to offset the binding of nerve agents (and preferential binding of agent VX) to RBC-AChE. For example, pretreatment with human plasma cholinesterase has protected laboratory animals from lethal and other acute toxic effects of VX exposure (monkeys in Raveh et al 1977; laboratory rodents in Ashani et al 1993). [Ashani, Y. et al 1993. *Cholinesterase prophylaxis against organophosphorous poisoning.* AD-A277096. US Army Medical Research, Development, Acquisition and Logistics Command, Ft. Detrick, MD; Raveh, L, et al 1997. "The stoichiometry of protection against soman and VX toxicity in monkeys pretreated with human butyrylcholinesterase." *Toxicol. Appl. Pharmacol.*]

Thus, variability in plasma cholinesterase activity is a parameter of concern for characterization of populations susceptible to VX exposure.

These additional references can be added to the text of Section 4.5.3 for clarification.

Comment 13: Section 4.5.5 Concurrent Exposure Issues Multiple Exposure Through Different Exposure Pathways: The minute-concentration for mice from Koon et al. (1960) is incorrectly cited as 11.5 mg-min/m^3. The correct value is 4 mg-min/m^3.

Proposed Action: Make the correction.

RESPONSE TO SPECIFIC COMMENT 13: Cross-check with the document developer's copy of the NRC (1997) report, p. 51, para 3 [Section entitled "Percutaneous Vapor Exposure; Lethal Effects (LCt_{50})"], reveals the following text:

"The percutaneous toxicity of VX vapor was investigated in mice and goats.....The LCt_{50} was 11.5 mg-min/m^3 for mice and 100 to 150 mg-min/m^3 for clipped goats (Koon et al. 1960)."

It appears that the commentor mis-read the text, which specifically addresses PERCUTANEOUS vapor exposure only. In a later portion of the NRC (1997) document (p. 53, para 5 [Section entitled "Inhalation Vapor Exposure; Lethal Effects LCt_{50}"]), the text reads:

"The vapor toxicity of VX was also investigated in mice for whole-body or head-only exposures (Koon et al. 1960). For a 10-min exposure, the LCt_{50} for whole-body exposure in mice was 4 mg-min/m^3."

The TSD text on PERCUTANEOUS vapor exposure correctly quotes the NRC (1997) summary of the Koon et al (1960) findings. No text change warranted.

Comment 14: Appendix A, Scaling. No data specific to VX is provided to support the value of n = 2 for in the equation $C^n \times t = k$ used for time scaling. The value of two is based on GB. What is the default value for n in the absence of data? Is the value of 2 protective?

Proposed Action: Evaluate the appropriateness of the n = 2 and document why this value is protective of human health in the absence of data specific to VX.

RESPONSE TO SPECIFIC COMMENT 14:

As earlier pointed out in the Response to General Comment 1, the NAC and the commentor are in agreement on the need for more and better experimental data characterizing agent VX vapor toxicity. As a consequence, the NAC has identified specific research studies whose performance would reduce uncertainties in the estimate, and declared the AEGL estimates for agent VX to be temporary and subject to re-evaluation by the NAC in 3 years. In this manner, the NAC has acknowledged existing data gaps and has encouraged collection of new data to elucidate dose response curves and determination of the value of "n." .

The estimate of "n" currently used in developing proposed AEGL estimates for agent VX vapor is supported by existing experimental data and represents a reasonable approach that should stand until additional and well-conducted experimental data permit an alternative determination. It is recommended that no change in the value of "n" used in the AEGL determinations be made at this time.

Comment 15: Appendix A, Uncertainty Factors. The factor of 10 for intraspecies is appropriate.

RESPONSE TO SPECIFIC COMMENT 15: Agree. No response required.

Comment 16: Appendix A, Modifying Factor. The proposed modifying factor of three for limitations in VX database used for all AEGLs in inadequate. As noted in the Executive Summary, "The few studies available are historical, and are considered nonverifiable due to flawed study design, poor sampling techniques, or suspect contamination of sampling and detection apparatus". Statements in the section for AEGL-3 include: "The NAC noted that an earlier report by the National Research Council (NRC, 1997) included an evaluation of the same VX toxicity data base, and had recommended at that time that additional research was needed to more fully characterize the toxicity of VX vapor.... To acknowledge the significant gaps in the

data base for this nerve agent, the NAC considers the proposed AEGL values to be temporary in nature and subject to re-evaluation in 3 years." The lack of data and predicted steep dose-response curve warrant a full data base uncertainty factor of 10 to avoid under-predicting the toxic effects of VX.

Proposed Action: Whether it is called a data base uncertainty factor or a modifying factor for data base uncertainty, change the value to 10.

RESPONSE TO SPECIFIC COMMENT 16:Use of the full default value of 10 is reserved for cases where there are truly no data; that is the purpose of a default value. In the case of agent VX, despite the acknowledged database limitations, much is known about the agent mechanism of action, and comparative experimental data exist for humans as well as the rat and rabbit. In the presence of limited data, the NAC considers use of a MF of 3 to be appropriate at this time. It is recommended that no change in the value of the modifying factor used in the present determinations be made at this time.

Comment 17: Appendix A. AEGL-3. The relative potency of 10 for the toxicity of VX compared to GB is not sufficient if 10 is the appropriate relative potency for the AEGL-1 and AEGL-2. The critical effect for the AEGL-1 and AEGL-2 is miosis. For miosis, the substantially greater dermal hazard of VX compared to GB is not likely relevant. However, for the lethality endpoint used for the AEGL-3, the significant amount of dermal absorption of VX compared to GB (e.g., see NRC, 1997) should be accounted for in determining the relative potency for the lethality endpoint.

Proposed Action: Re-evaluate the appropriateness of the relative potency of 10 for the AEGL-3)

RESPONSE TO SPECIFIC COMMENT 17: Please see response to General Comment 1.

References.

Bittner, C. 2000 Letter to Dr. Paul Joe, CDC, Comments on Proposed Airborne Exposure Limits for the G-Chemical Agents and VX. September 21, 2000.

Bramwell, E.C.B., W.S.S. Ladell, and R.J. Shepard. 1963. *Human Exposure to VX Vapour*, PTP830

Callaway, S. and P. Dirnhuber. 1971. *Estimation of the Concentration of Nerve Agent Vapour Required to Produce Measured Degrees of Miosis in Rabbit and Human Eyes.* CDE, July. Porton Down

DHHS, 2000. Department of Health and Human Services Centers for Disease Control and Prevention. Verbatim Transcript of the Public Meeting of the Review of Safe Airborne Exposure Limits for Nerve Agents GA, GB, and VX. Atlanta, Georgia, August, 2000.

Mioduszewski, R.J., S.A. Reutter, L.L. Miller, O.J. Olajos, and S.A. Thomsom. 1998. *Evaluation of Airborne Exposure Limits for G-Agents: Worker and General Population Exposure Criteria.* April, 1998 and 2000 Addendum

NRC (National Research Council, Committee on Toxicology). 1997. *Review of Acute Human-Toxicity Estimates for Selected Chemical Warfare Agents*. National Academy Press, Washington, D.C.

USACHPPM (United States Army Center for Health Promotion and Preventive Medicine) TG18. United States Army Center for Health Promotion and Preventative Medicine. *Detailed and General Facts About Chemical Agents - TG 218*

USEPA (United States Environmental Protection Agency), 2000. *The Use of Data on Cholinestesterase Inhibition for Risk Assessements of Organophorus and Carbamate Pesticides*. Office of Pesticide Programs. August 18, 2000.

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00312

C-006

SPP

"Rogers, Harvey" <hxr2@cdc.gov> on 05/31/2001 01:44:34 PM

To: NCIC OPPT/DC/USEPA/US@EPA
cc:

Attachment 21

Subject: Docket OPPTS-00312

Attached are CDC's comments on the above docket. Hardcopy is also forthcoming.

<<aegl01.txt>> <<aegl01.wpd>>

If you have any questions please call Harvey Rogers at 770 640-6338 or reply to this E-mail.

aegl01.txt aegl01.wpd

May 30, 2001

Barbara Cunningham
Acting Director
Environmental Assistance Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket Control Number OPPTS-00312

Dear Ms. Cunningham:

The Centers for Disease Control and Prevention (CDC) is engaged in a review of proposed airborne exposure levels for two of the eighteen chemicals addressed in the above-referenced document. These two chemicals are isopropyl methyl phosphonofluoridate (GB) and O-ethyl-S-(isopropylaminoethyl) methyl phosphonothiolate (VX). The CDC is conducting this review as a part of its chemical warfare agent demilitarization oversight functions. More specifically, CDC is reviewing the Army's proposed Worker Population Level (WPL) and General Population Level (GPL) for both of these agents. There has been no indication that the worker and general population exposure limits recommended by the CDC in 1988 have been less than fully protective. However, CDC believes it is prudent to periodically review the latest relevant health studies using the latest risk assessment techniques to determine if any changes to the exposure limits are warranted.

In general, the CDC is working with the same methodology and toxicity data described in the proposed Acute Exposure Guideline Levels (AEGLs) document. Accordingly, we do make the observation that we believe the approach used by the National Advisory Committee to develop the proposed AEGLs is appropriate. One significant difference between CDC's and EPA's efforts, however, is the WPLs and GPLs being considered by CDC are targeted to exposure levels where no demonstrable health effects would be anticipated; whereas the AEGLs describe exposure levels where varying severity levels of health impact are expected. Because of variations in ranges of exposure and the varied intended uses of the AEGLs, WPLs, and GPLs, it is reasonable to anticipate that some subjective factors used in deriving these exposure limits might vary from application to application.

Given that the CDC is still working on its proposal for the WPLs and GPLs for agents GB and VX, we believe that it is premature for CDC to provide comments on the proposed AEGLs. CDC expects to solicit comments through the Federal Register for its proposed limits within the

next several months. In the interest of using the best possible information for CDC's proposed exposure levels, we would very much appreciate being apprized of any new information or significant insights that might be obtained as a result of this solicitation for comments by EPA. We, of course, would share similar insights with EPA resulting from our forthcoming solicitation.

We believe that the above suggested sharing of information is in the best interest of the human health protection goals shared by both our agencies. If EPA agrees, we would like to establish key contact points between each of our agencies to facilitate the exchange of information.

We appreciate this opportunity to open this dialogue and look forward to communicating further with EPA as described above.

Sincerely,

Paul Joe, D.O.
Senior Medical Advisor

May 30, 2001

Barbara Cunningham
Acting Director
Environmental Assistance Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket Control Number OPPTS-00312

Dear Ms. Cunningham:

The Centers for Disease Control and Prevention (CDC) is engaged in a review of proposed airborne exposure levels for two of the eighteen chemicals addressed in the above-referenced document. These two chemicals are isopropyl methyl phosphonofluoridate (GB) and O-ethyl-S-(isopropylaminoethyl) methyl phosphonothiolate (VX). The CDC is conducting this review as a part of its chemical warfare agent demilitarization oversight functions. More specifically, CDC is reviewing the Army's proposed Worker Population Level (WPL) and General Population Level (GPL) for both of these agents. There has been no indication that the worker and general population exposure limits recommended by the CDC in 1988 have been less than fully protective. However, CDC believes it is prudent to periodically review the latest relevant health studies using the latest risk assessment techniques to determine if any changes to the exposure limits are warranted.

In general, the CDC is working with the same methodology and toxicity data described in the proposed Acute Exposure Guideline Levels (AEGLs) document. Accordingly, we do make the observation that we believe the approach used by the National Advisory Committee to develop the proposed AEGLs is appropriate. One significant difference between CDC's and EPA's efforts, however, is the WPLs and GPLs being considered by CDC are targeted to exposure levels where no demonstrable health effects would be anticipated; whereas the AEGLs describe exposure levels where varying severity levels of health impact are expected. Because of variations in ranges of exposure and the varied intended uses of the AEGLs, WPLs, and GPLs, it is reasonable to anticipate that some subjective factors used in deriving these exposure limits might vary from application to application.

Given that the CDC is still working on its proposal for the WPLs and GPLs for agents GB and VX, we believe that it is premature for CDC to provide comments on the proposed AEGLs.

CDC expects to solicit comments through the Federal Register for its proposed limits within the

next several months. In the interest of using the best possible information for CDC's proposed exposure levels, we would very much appreciate being apprized of any new information or significant insights that might be obtained as a result of this solicitation for comments by EPA. We, of course, would share similar insights with EPA resulting from our forthcoming solicitation.

We believe that the above suggested sharing of information is in the best interest of the human health protection goals shared by both our agencies. If EPA agrees, we would like to establish key contact points between each of our agencies to facilitate the exchange of information.

We appreciate this opportunity to open this dialogue and look forward to communicating further with EPA as described above.

Sincerely,

Paul Joe, D.O.
Senior Medical Advisor

RESPONSE: The NAC welcomes dialogue with the Chemical Demilitarization Branch of the National Center for Environmental health, CDC, and will be pleased to share information and analyses with the Branch on a continuing basis.

CONTENT SUMMARY: There is no issue of disagreement. The CDC Chemical Demilitarization Branch is supportive of the NAC effort, and wished to inform the NAC that the Branch is presently involved in a related area–that of developing long-term occupational and general public exposure guidelines for airborne chemical warfare agents. Further, the Branch wished to state that they could benefit from being made aware of any additional research or insight identified in the FR comment process, and requested communication of same from the NAC.

The document developer has coordinated with Dr. Mark McClanahan, NAC member and staff scientist at the National Center for Environmental Health(CDC), in responding to this comment. Dr. McClanahan has made contact with Dr. Paul Joe for follow up to these comments.

00312
C-009

2pp

"Lantzer, Paula K LTC SBCCOM"
<paula.lantzer@SBCCOM.APGEA.ARMY.MIL> on 06/01/2001 09:36:14 AM

To: NCIC OPPT/DC/USEPA/US@EPA
cc: "Myirski, Michael M SBCCOM" <michael.myirski@SBCCOM.APGEA.ARMY.MIL>, "'veronique.hauschild@apg.amedd.army.mil'" <veronique.hauschild@apg.amedd.army.mil>, "Fisher, Denzel HQDA" <denzel.fisher@hqda.army.mil>

Subject: AEGL Concur

aegl_nerve_csepp.doc

Attachment 22

48512

Comment to: 2 May 2001 issue of the Federal Register (vol. 66, no. 85, pp 21940-21964, Docket Control Number OPPTS-00312)

As the Army proponent for emergency planning criteria for the U.S. stockpiled chemical warfare agents, I have coordinated an Army review of the specified AEGLs for G-series and VX nerve agents, and concur with stated values.

Signed,

LTC Paula K. Lantzer

Product Manager, Chemical Stockpile Emergency Preparedness Program
USA SBCCOM

Attachment 23

FEDERAL REGISTER COMMENTS RECEIVED ON

PROPOSED AND PROPOSED TEMPORARY NERVE AGENT AEGL ESTIMATES

(66*FR* 21940-21964, 2 MAY 2001)

NAC/AEGL-21
U.S. Dept. of Transportation
DOT Headquarters/Nassif Bldg., Rms 8236-8240
400 7th Street, SW
Washington, DC

June 11-13, 2001

CHEMICAL DEMILITARIZATION BRANCH (Dr. Paul Joe)
NATIONAL CENTER FOR ENVIRONMENTAL HEALTH
CENTERS FOR DISEASE CONTROL
DHHS

- **No issue of disagreement**
- **Branch is supportive of NAC effort and approach, interested, and is opening avenue of communication**
- **Branch is developing long-term occupational and general public exposure guidelines for same agents, and wishes to mutually share insight and information with NAC and AEGL process**
- **Following receipt of CDC comment, Mark McClanahan communicated with Paul Joe for clarification and exchange**

HAZARDS CONTROL (Dr. Monty Herr)
LAWRENCE LIVERMORE NATIONAL LAB
UNIVERSITY OF CALIFORNIA
LIVERMORE, CA

Q: Recommend inclusion of additional MF for incomplete agent-specific database for nerve agents GA, GD and GF in comparison to database for agent GB. Seems to be inconsistency with application of MF for agent VX.

A: Database for G-agents as group considered complete in that

- **experimental data for multiple species, including human (non-lethal)**
- **documented non-lethal and lethal endpoints exhibiting exposure-response data**
- **known mechanism of toxicity; all endpoints represent response continuum to anticholinesterase exposure**
- **no uncertainties regarding reproductive/developmental effects, or carcinogenicity**

Since mechanism of action same (cholinesterase inhibition), data uncertainty reduced and target organ effects similar but differ in magnitude.

Variability in target organ response sufficiently addressed by relative potency factors applied between GB and other G-agents, and is endpoint-specific.

Database for agent VX considered much less complete than composite database for G-series agents. Thus application of MF = 3 warranted.

Consistency in logic maintained.

HAZARDS CONTROL (Dr. Monty Herr)
LAWRENCE LIVERMORE NATIONAL LAB
(cont'd)

Q: Selection of SFEMG changes as a protective definition of AEGL-2 effects suggests that Intraspecies UF < 10 warranted

A: Option considered but rejected by NAC majority in favor of UF = 10

Q: Provided additional source citations of technical and memo reports from Defence Research Establishment Suffield (Canada) and TNO Prins Maurits Laboratory, The Netherlands

A: Citations accepted with thanks and will be incorporated as possible. Please note that current primary VX concern of Office of Army Surgeon General is focused on VX vapor rather than VX aerosol. VX aerosols may be separately evaluated in the future.

Q: Editorial suggestions regarding word selections, expanded treatment of certain source material, alternate explanations of experimental observations

A: Necessary changes will be made

DIVISION OF SOLID AND HAZARDOUS WASTE (Christopher Bittner)
STATE OF UTAH
SALT LAKE CITY, UT

AGENT VX

Q: Overall concern that single relative potency factor ("of 10") comparing agent VX to agent GB not supported by information presented in Tables of VX TSD and that the "relative potency should be derived based on the experimental data that match...exposure regime and toxicological endpoint."

A1: NAC and commentor are in agreement on need for more and better data characterizing VX vapor toxicity. As a consequence

- **NAC identified research studies specifically designed to reduce uncertainties in estimates**
- **NAC declared VX AEGL estimates "temporary" and subject to re-evaluation in 3 years**
- **NAC acknowledged existing data gaps and made practical suggestions for collection of specific new data to elucidate dose-response curves**

A2: Commentor is considering the range of relative potency ratios cited in Tables of TSD without making any distinction between primary (text boldface) and secondary sources. NAC SOPs require use of primary source data for AEGL derivations; verifiable EXPERIMENTAL data for humans, rats and rabbits provide less variable range of ratios; range = 4.2 to 33. Commentor's remarks made without complete knowledge of the NAC SOPs.

NAC determined that best available primary study (rabbit pupil area decrement; Calloway and Dirnhuber 1971) and best endpoint (90 % pupil area decrement; has operational significance for emergency response and is more definitive) provides relative potency ratio of 12. Until additional data from well-conducted experimental studies are available, current relative potency approach (RP = 12) reasonable, supported by existing experimental data, and meets requirements of the SOPs.

A3: Commentor in error by assuming a relative potency factor of 10.

DIVISION OF SOLID AND HAZARDOUS WASTE (Christopher Bittner)
STATE OF UTAH
SALT LAKE CITY, UT
(cont'd)

Q: Commentor considers that the USEPA (2000) report *Science Policy on Use of Data on Cholinesterase Inhibition.*. does not emphasize use of clinical signs/symptoms (humans) and behavioral/physiological effects (humans and animals) as more significant than measures of cholinesterase (activity) as critical endpoint

A: The *Science Policy* considers cholinesterase inhibition as a useful biomarker of exposure, but that most direct evidence of adverse consequences for these compounds to be clinical signs and symptoms in humans and behavioral or physiological effects in humans and animals. Commentor was directed to specific pages in the *Science Policy*.

Q: Commentor recommends dosimetric adjustment for AEGL-3 determination

A: As is true for all AEGL determinations, the NAC/AEGL does not make dosimetric adjustments for attaining human equivalent doses. Although a number of methods have been proposed by various bodies and individual investigators, there is insufficient validation with experimental data for determination of most appropriate and scientifically sound approach. Until such time, the AEGL process will refrain from performing dosimetric adjustments for estimating human equivalent doses.

The position of the NAC is documented in Sect. 2.4 of the SOPs.

DIVISION OF SOLID AND HAZARDOUS WASTE (Christopher Bittner)
STATE OF UTAH
SALT LAKE CITY, UT
(cont'd)

Q: Commentor questions relevance of plasma cholinesterase as a variable of concern in determining susceptibility to VX exposure.

A: While biological role of plasma cholinesterase incompletely known at present, experimental data demonstrate that pretreatment with plasma cholinesterase has protected non-human primates and laboratory rodents from lethal and non-lethal acute effects of VX exposure. Citations to these specific papers provided in detailed response to commentor. These references document that variability of plasma cholinesterase activity is an experimentally validated parameter of concern for characterizing populations susceptible to VX exposure. Author of technical support document will augment text treatment of these references to emphasize point.

Q: Estimate of n=2 is not based on VX-specific data.

A: NAC and commentor are in agreement on need for more and better data characterizing VX vapor toxicity. As a consequence

- **NAC identified research studies specifically designed to reduce uncertainties in estimates**
- **NAC declared VX AEGL estimates "temporary" and subject to re-evaluation in 3 years**
- **NAC acknowledged existing data gaps and made practical suggestions for collection of specific new data to elucidate dose-response curves and determination of "n"**

Until additional data from well-conducted experimental studies are available, current value of "n" (=2) is reasonable, supported by existing experimental data, and meets requirements of the SOPs.

DIVISION OF SOLID AND HAZARDOUS WASTE (Christopher Bittner)
STATE OF UTAH
SALT LAKE CITY, UT
(cont'd)

Q: Commentor considers that MF should be equal to 10 and not 3.

A: Use of the full default value of 10 is reserved for cases where there are truly no data. In the case of agent VX, despite acknowledged database limitations, much is known about mechanism of action, and comparative experimental data exist. In the presence of limited data, the NAC considers use of a MF = 3 to be appropriate at this time. This is another reason why the NAC has determined that VX estimates should be considered "temporary " and re-evaluated in 3 years.

Q: Typographical errors noted, editorial suggestions regarding word selections and clarity

A: Typographical error identification accepted with thanks; necessary changes for this and editorial suggestions will be made as needed

PRODUCT MANAGER (LTC Paula Lantzer)
CHEMICAL STOCKPILE EMERGENCY PREPAREDNESS PROGRAM
U.S. ARMY SOLDIER and BIOLOGICAL CHEMICAL COMMAND
U.S. DEPARTMENT OF THE ARMY

- **Official Concurrence**

"As the Army proponent for emergency planning criteria for the U.S. stockpiled chemical warfare agents, I have coordinated an Army review of the specified AEGLs for G-series and VX nerve agents, and concur with the stated values."

BASIC ACRYLIC MONOMER MANUFACTURERS, INC.
1250 Connecticut Ave., N.W., Suite 700, Washington, DC 20036
Office: (202) 637-9040 Facsimile (202) 637-9178

Attachment 24

May 31, 2001

JUN 12 2001

Mr. Paul S. Tobin
Designated Federal Officer
Office of Prevention, Pesticides, and Toxic Substances (7406)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Subject: Comments on the proposed AEGL values for acrylic acid published in the Federal Register on May 2, 2001 (Docket Control Number OPPTS-00312)

Dear Mr. Tobin:

General Comments

We would like to commend the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) for its thorough evaluation of the relevant scientific information for the establishment of AEGL values for a wide variety of substances exhibiting very different toxicological profiles. The Standard Operating Procedures developed by the NAC/AEGL committee are obviously a valuable resource for data evaluation for establishing AEGLs. However, we would like to encourage the committee to "step back and see if the numbers make sense" in the context of the relevant substance-specific datasets at the end of the standard setting process.

We would also like to encourage the committee to consult the information that is being collected for the European Union (EU) Risk Assessments for industrial chemicals when they are available. The EU risk assessments are valuable resources for human exposure information that has not been readily available. In addition, the EU risk assessments list exposure limits that have been established by other authoritative bodies, and these may provide useful perspectives relative to the proposed AEGL values.

General Comments on the Dose Response for Effects Associated with Inhalation Exposure to Acrylic Acid

The specific issue that we would like to address is the nasal and eye irritant, acrylic acid. As noted in the NAC draft Technical Support Document for acrylic acid (Public Draft; February, 2001), the only non-lethal adverse effects observed in any animal species following inhalation exposure to acrylic acid in acute and subchronic exposures at concentrations up to 100 ppm were cytotoxicity in the nasal olfactory epithelium (observed in all species evaluated). At vapor concentrations of 100-400 ppm, nasal toxicity was accompanied by watery discharges from the eyes and nose indicative of irritation, restlessness, and eye blinking or eyelid closure in some studies. Credible mortality studies have only produced lethal effects at inhalation exposure concentrations

in excess of 1000 ppm. NOAELs typically observed in a wide range of acrylic acid inhalation studies have ranged from 5-25 ppm with no toxic effects observed in any species at exposure concentrations less than 5 ppm. As noted in the Technical Support Document, aside from the nasal and eye irritation at lower inhalation exposure concentrations (useful for setting an AEGL-1 value) and mortality observed at very high concentrations (useful for setting an AEGL-3 value), there is no reported systemic toxicity and very little else to use as a basis for setting an AEGL-2 value.

Comments on an Additional Acute Inhalation Study with Primates

In addition to the studies cited in the Technical Support Document for acrylic acid, we are submitting an additional inhalation study. The attached report is for the in-life portion of an inhalation study with Cynomolgus monkeys. The study design is basically the same as that reported for rats in Frederick et al. (1998) as cited in the Technical Support Document (either 3 or 6 hr exposure at 75 ppm acrylic acid vapor relative to a control group; 3 animals/group; exposure to ethyl acrylate vapor was also evaluated in the study). The animals were exposed using an exposure helmet that allowed uniform exposure of the entire head. The study report is incomplete only in that the histopathology report has not been completed by the academic group collaborating on the study (although a Society of Toxicology abstract reporting his preliminary findings is attached). We have encouraged the pathologist to complete his report, and we anticipate that he will publish his findings upon completion.

The study was designed to evaluate the susceptibility of primate olfactory epithelium to cytotoxicity induced by acrylic acid exposure relative to rodent olfactory epithelium. Mapping of the histopathology induced in the primate nasal cavity was an important part of the experimental design. Note that Cynomolgus monkeys have an elongated nasal cavity with a very large olfactory region covering the posterior region of the nasal cavity in a very similar manner to rodents (although the turbinate structure is quite different). Clinical observations were recorded before and after exposure. Upon necropsy after exposure, the major organs were evaluated for abnormal findings. **The in-life report indicates that inhalation exposure of Cynomolgus monkeys to 75 ppm acrylic acid vapor for either 3 or 6 hr resulted in no clinical signs of toxicity and no treatment related findings on gross pathology evaluation of the major organs. An animal exposed to ethyl acrylate vapor in the same experiment was reported to demonstrate an increased rate of eye blinking, but the animals exposed to acrylic acid did not exhibit this response.** The SOT abstract indicates that olfactory cytotoxicity was observed that was comparable to that observed in the rat nasal cavity under the same exposure protocol. This suggests that the tissue dosimetry and susceptibility is comparable between these two species.

Comments Regarding Acute Inhalation Exposures and Olfactory Toxicity

We would like to address a comment that we believe to be in error in the technical support document. Unique among neuronal tissues, nasal olfactory epithelium is characterized by a normal rate of cellular turnover and can regenerate following damage. Loss of olfactory epithelium that is accompanied by replacement with respiratory

epithelium is a well-documented component of human aging (e.g. Loo et al., 1996, Paik et al., 1992, Talamo et al., 1994 and references cited therein). These references note that olfactory sensitivity declines with age in humans. In addition, olfaction is compromised by allergies, rhinitis, and a variety of other common disease states. Although lack of normal olfaction is an important 'quality of life' issue, it is not generally associated with an 'impaired ability to escape.'

An extensive set of studies by Youngentob and Schwob and others (some representative papers are listed below) have demonstrated that the olfactory epithelium can recover following an acute inhalation exposure that causes extensive olfactory cytotoxicity (e.g., with >90-95% of the olfactory epithelium destroyed with methyl bromide vapor). In addition, these authors have demonstrated that the olfactory epithelium can exhibit a considerable amount of cytotoxicity and yet still retain sufficient functional capacity to adequately perform a series of olfaction tests. Therefore, although damage to the olfactory epithelium is not desirable and should be avoided, a single acute exposure would not be predicted to result in a permanent functional deficit. The Technical Support Document correctly reports that recovery of damaged olfactory epithelium has been demonstrated following inhalation exposure to acrylic acid vapors in an toxicology study (Lomax et al., 1994).

Human Occupational Exposure Monitoring Data

Concerning ongoing human inhalation exposure to acrylic acid, the current EU risk assessment provides additional valuable information. The document lists occupational exposures for a wide range of tasks that range from 0.01 to 5 ppm with a 90th percentile at 1 ppm. Short term exposure values ranged from 0.01 to 62.4 ppm. The EU risk assessment reports occupational exposure limits for 9 countries (United Kingdom, Switzerland, Sweden, United States, Belgium, Austria, Netherlands, Denmark, and France) as ranging from 2 to 10 ppm with short term exposure limits in 3 countries (United Kingdom, Sweden, and France) ranging from 10 to 20 ppm. The widespread adoption of these occupational exposure limits without reports of adverse effects suggests that humans can be exposed to acrylic acid vapors in this concentration range for long periods of time without harm. Notably, there is an absence of reports linking human exposure to acrylic acid vapors with mortality.

In addition to the EU documentation of human exposures, the member companies of the Basic Acrylic Monomer Manufacturers (BAMM) and the European Basic Acrylate Manufacturers (EBAM) have conducted air monitoring studies of acrylic acid in the workplace. A summary of these data from for the last 20 years is attached. The 8 hr TWA monitoring results have ranged from 0.003 ppm (or a nondetect at the limit of detection of the analytical method at the time) to 4.27 ppm with a single outlier at 26 ppm. The median TWA measurement was 0.15 ppm. Of the total of 259 samples, 8% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection above 1 ppm). The short term exposure limit (typically 15 min STEL) monitoring results ranged from <0.001 ppm to 63 ppm (or a nondetect at the limit of detection of the analytical method at the time). The median STEL measurement was 0.5

ppm. Of the total of 631 samples, 34% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection equal to or greater than 1 ppm). In addition, the companies monitor the health of their workers and keep a record of adverse medical reports associated with chemical exposure. As described in the attached reports from Corporate Medical Departments, employee exposures to acrylic acid within the 2-5 ppm 8 hr TLV exposure limits (including both current and historical TLV limits) have not resulted in employee complaints of nose or eye irritation. Note that workers are encouraged to report safety problems in the workplace including chemical exposures that result in adverse health effects. The few reports of eye or nose irritation that were recorded have related to spills or accidents that produced unusual exposure scenarios (described in an attached letter). These accidents undoubtably involved inhalation exposures significantly in excess of the TLV, although the transient nature of the incidents prevented exposure monitoring. In all cases, rapid and complete recovery was noted from the signs of irritation that were reported. Given these data from the longterm use of acrylic acid in industry, it may be concluded that the chronic exposure of workers to acrylic acid under the current ACGIH TWA exposure limit of 2 ppm has not produced an adverse effect on health.

AEGL-1

Acrylic acid is a "contact site irritant" that exerts its effects based upon the concentration of the vapor that is absorbed into the contact site tissue. The initial clinical signs of irritation typically occur relatively quickly, and would not be expected to dramatically increase during the course of a single exposure of 8 hr or less. Given the widespread adoption of 2 ppm as an occupational exposure limit, we suggest that a value no lower than 2 ppm be adopted as an AEGL-1 value (nondisabling) for an 8 hr exposure. The short term exposure limit (15 minute STEL) that is commonly used in industry is 6 ppm, and we propose this value as the exposure limit for 10 min exposure. Exposure limits for other times would be interpolated between these values. This recommendation is based upon nasal irritation (minimal olfactory toxicity) that might be observed in either animals or humans following inhalation exposure to acrylic acid in the 5-25 ppm concentration range. No other clinical signs or indications of pathology have been observed with mice, rats, or rabbits in this dose range. Given the consistency in effect across species (including rats relative to monkeys at 75 ppm) and lack of toxicity reported with the current occupational exposure limits (ranging from 2 to 10 ppm), we propose a species to species conversion factor of 1. Given the inherent variability in individual response, we propose an intraspecies extrapolation factor of 3. The Preface to the Technical Support Document provides a definition of AEGL-1 that is consistent with this proposed value. In addition, the Preface notes that "Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects." The odor detection threshold of acrylic acid clearly falls within this provision.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	6.0 ppm (18.0 mg/m^3)	5.0 ppm (15.0 mg/m^3)	4.0 ppm (12.0 mg/m^3)	3.0 ppm (9.0 mg/m^3)	2.0 ppm (6.0 mg/m^3)

AEGL-3

Regarding AEGL-3 values (lethal) for acrylic acid, we note that there are no credible reports of acute lethality in any species at inhalation exposure concentrations less than 1000 ppm. In addition, repeat-dose inhalation studies with acrylic acid have repeatedly been conducted with various animal species at concentrations up to approximately 250 ppm without lethality. Addressing the issue of interspecies extrapolation between rodents and primates, the attached monkey study was conducted at inhalation exposures of 75 ppm without any clinical signs of toxicity. No reports link human inhalation exposure to acrylic acid with lethality despite its widespread and long term use in industry. Under these circumstances, we do not believe that a large species to species conversion factor is justifiable --- particularly, since definition of the AEGL values based upon vapor concentration automatically introduces an allometric scaling factor due to the inherent differences in respiratory physiology between species. AEGL-3 values below 250 ppm lack scientific credibility in the context of this extensive database. We note that in the best designed study for providing AEGL-3 data that is available (Hagan and Emmons, 1988), no lethality was observed at the highest vapor concentration that could be generated (2142 ppm). Therefore, we suggest an intraspecies conversion factor of 3, a species to species conversion factor of 1, and an AEGL-3 (lethal) value consistent with the AIHA ERPG-3 value of 750 ppm for 1 hr exposures. This AEGL-3 value would decrease to approximately 500 ppm for an 8 hr exposure and increase to approximately 1500 ppm for a 10 minute exposure.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3 (Lethal)	1500 ppm (4500 mg/m^3)	1200 ppm (3600 mg/m^3)	750 ppm (2250 mg/m^3)	625 ppm (1875 mg/m^3)	500 ppm (1500 mg/m^3)

AEGL-2

The establishment of an AEGL-2 value (disabling) is problematic, since the available data on the toxic effects associated with acrylic acid exposure do not provide endpoints that are very appropriate. The blinking reported in rabbits in the Neeper-Bradley et al. (1997) study is hardly sufficient (study used as a basis for the AEGL-2 proposal at the July, 2000 NAC/AEGL meeting), since it could be argued that eye blinking or squinting (blepharospasm) of a sendentary animal in a toxicology study does not necessarily represent a disabling effect. A functional evaluation to determine whether the animals eyesight was impaired would have been much more convincing. The slides presented at the NAC/AEGL meeting on July 26-28, 2000, appeared to draw comparisons to the increased rate of blinking or squinting observed in the Neeper-Bradley et al. (1997) study with the dramatic effects of the very potent lacrimators used in tear gas. This comparison is inappropriate due to the very high potency of the agents used in tear gas relative to the much weaker effects exhibited by acrylic acid vapors; i.e., clinical signs of the range and magnitude induced by tear gas have not been reported in either animal studies or human occupational exposures with acrylic acid.

The Technical Support Document for this AEGL/NAC meeting refers to a single dose acute inhalation study with rats exposed to acrylic acid at 75 ppm for either 3 or 6 hr

(Frederick et al., 1998). This study was conducted as part of the validation process for a nasal dosimetry model for acrylic acid. An inhalation study with the same basic experimental design using Cynomolgous monkeys is attached to these comments. In these studies, the cytotoxicity that was observed in the olfactory epithelium of the exposed animals was relatively comparable across species. Although clinical signs were not recorded in the acute rat study, prior repeat-dose studies with rats at 75 ppm have documented no discernable changes in posture or appearance at this vapor concentration (Miller et al., 1981). The monkey study also did not report clinical signs of irritation or distress at the 75 ppm exposure concentration. The Technical Support Document invokes the use of time scaling in a $C^n \times t = k$ with $n = 1.8$ based upon the dose response curve for lethality from the Hagan and Emmons (1988) study and a total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies). The resulting proposed AEGL-2 values for acrylic acid range from 6.4 ppm (8 hr) to 30 ppm (10 min). These proposed AEGL-2 values are in the range of effects that range from NOAELs to mild and reversible nasal irritation in every species that has been evaluated. The effects that have been observed in this dose range clearly do not fall into the range of "irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape" which form the basis of the definition of an AEGL-2.

We propose an AEGL-2 value of 75 ppm for all time periods based on the following considerations: [1] the lack of eye blinking or squinting in rabbits at inhalation exposures of 77 and 61 ppm (Neeper-Bradley et al., 1997), [2] the lack of eye blinking or other clinical signs of toxicity in monkeys during an inhalation exposure of 75 ppm (attached study), [3] the cytotoxicity and nasal irritation observed in the 75 ppm acute inhalation exposure studies is reversible, not disabling, and it does not impair the ability to escape (see references on olfactory toxicity cited above), and [4] eye irritation (blinking and tearing) at inhalation concentrations above 100 ppm which might impede sight and escape. This would be accompanied by a species to species conversion factor of 1, since there does not seem to be much difference in response across several species tested. We propose an intraspecies variability factor of 1 based on the lack of severity of the response and the wide range of functional deficit that can be accomodated for this endpoint. In particular, this intraspecies variability factor is based upon the fact that 75 ppm is a NOAEL for blinking and tearing in multiple species, humans would be expected to exhibit either no effects or only mild effects for these symptoms in this dose range, and it takes a lot of tearing and blinking to incapacitate an individual to the extent that the ability to escape is impaired.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2 (Disabling)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)

Summary

In summary, our proposed AEGL values based upon the above considerations are the following:

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	6.0 ppm (18.0 mg/m^3)	5.0 ppm (15.0 mg/m^3)	4.0 ppm (12.0 mg/m^3)	3.0 ppm (9.0 mg/m^3)	2.0 ppm (6.0 mg/m^3)
AEGL-2 (Disabling)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)
AEGL-3 (Lethal)	1500 ppm (4500 mg/m^3)	1200 ppm (3600 mg/m^3)	750 ppm (2250 mg/m^3)	625 ppm (1875 mg/m^3)	500 ppm (1500 mg/m^3)

In closing, we note the recent publication of a mechanistic study that supplements the Custodio et al. (1998) study on acrylic acid that is cited in the Technical Support Document. The recent publication (Palmeira et al., 2000) is from the same research group and it further explores the proposed mechanism of cytotoxicity invoked by acrylic acid (induction of the mitochondrial permeability transition). The study demonstrates that this response is common for a wide range of short-chain carboxylic acids. We hope that you find the additional data that we are submitting useful in your deliberations, and we encourage your evaluation of the proposed AEGL values for acrylic acid in the context of its safe use in industry for many years.

With our regards,

Clay B. Frederick, Ph.D., DABT
Representing the Technical Committee
of the Basic Acrylic Monomer Manufacturers, Inc.
and the
European Basic Acrylate Manufacturers

The Basic Acrylic Monomer Manufacturers Inc. (BAMM) is an industry trade association, promoting the safe manufacture, handling and use of the basic acrylic monomers by addressing product aspects related to human health, environmental safety and associated regulatory issues.

Members of the Basic Acrylic Monomer Manufacturers, Inc.:

ATOFINA Chemicals, Inc.
BASF Corporation
Celanese Ltd.
The Dow Chemical Co.
Rohm and Haas Co.

Members of the CEFIC European Basic Acrylate Manufacturers (EBAM):

ATOFINA
BASF AG
Celanese GmbH
Rohm and Haas Co.
Chemicke Zavody Sokolov
Stockhausen GmbH

Some representative references on the structure and normal turnover of human olfactory epithelium including observations on the loss of olfactory epithelium on aging:

Loo AT, Youngentob SL, Kent PF, Schwob JE (1996). The aging olfactory epithelium: Neurogenesis, response to damage, and odorant-induced activity, INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, 14:881-900.

Paik SI, Lehman MN, Seiden AM, Duncan HJ, Smith DV (1992). Human olfactory biopsy - the influence of age and receptor distribution, ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY, 118: 731-738.

Talamo BR, Feng WH, Stockmayer M (1994). Human olfactory epithelium - normal patterns and types of lesions found in the genrall-population, INHALATION TOXICOLOGY, 6 (Suppl.): 249-275.

Some representative references on chemically-induced olfactory damage, functional evaluation of olfaction in animals with olfactory damage, and recovery of olfactory epithelium:

Schwob JE, Youngentob SL, Ring G, Iwema CL, Mezza RC (1999). Reinnervation of the rat olfactory bulb after methyl bromide-induced lesion: Timing and extent of reinnervation, JOURNAL OF COMPARATIVE NEUROLOGY, 412:439-457.

Huard JMT, Youngentob SL, Goldstein BJ, Luskin MB, Schwob JE (1998). Adult olfactory epithelium contains multipotent progenitors that give rise to neurons and non-neural cells, JOURNAL OF COMPARATIVE NEUROLOGY, 400:469-486.

Youngentob SL, Schwob JE, Sheehe PR, Youngentob LM (1997). Odorant threshold following methyl bromide-induced lesions of the olfactory epithelium, PHYSIOLOGY & BEHAVIOR, 62:1241-1252.

The current version of the EU risk assessment for acrylic acid, "Comprehensive Risk Assessment Report 2-Propenoic Acid," may be obtained from:
Bundesanstalt fur Arbeitsschutz und Arbeitsmedizin
Anmeldestelle Chemikaliengesetz
Friedrich-Henkel-Weg 1-25
44149 Dortmund
email: amst@baua.do.shuttle.de

The in-life report from an acute monkey inhalation study and an accompanying Society of Toxicology abstract are attached:
Michael J. Brooker and Michael E. Placke (1995). Final Report on Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA). Battelle/Columbus Study Number SC940138.

J. R. Harkema, J. K. Lee, K. T. Morgan, and C. B. Frederick (1997). Olfactory epithelial injury in monkeys after acute inhalation exposure to acrylic monomers. Abstract #576. The Toxicologist, 36, p. 113.

A recent mechanistic study exploring the mechanism of cytotoxicity of short-chain carboxylic acids (including acrylic acid):
C. M. Palmeira, M. I. Rana, C. B. Frederick, and K. B. Wallace (2000). Induction of the mitochondrial permeability transition in vitro by short-chain carboxylic acids, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 272: 431-435.

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REPLY TO
SAFETY, HEALTH & ENVIRONMENT
BOX 584
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ROHM AND HAAS COMPANY

May 30, 2001

Mr. Paul S. Tobin
Designated Federal Officer
Office of Prevention, Pesticides, and Toxic Substances (7406)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Subject: Comments on the proposed AEGL values for acrylic acid published in the Federal Register on May 2, 2001

Dear Mr. Tobin:

After reviewing the proposed AEGL values for acrylic acid published in the Federal Register, we request that the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances reassess the values chosen, using research data from inhalation studies (a number of studies exist using a number of species), and human data where available. We believe the proposed AEGL-1 value of 1ppm for acrylic acid is not consistent with toxicology information from animal studies and human observations that indicate that 8hr TWA concentration of 2 - 5 ppm does not cause respiratory or eye irritation as defined for AEGL-1, even with chronic exposure. Indeed, the 2 - 10 ppm permissible exposure limit used by most countries is believed to protect workers who are chronically exposed throughout a 40-year working career from all deleterious health effects. We respectfully request that the committee re-evaluate the scientific information before establishing an AEGL-1 value for acrylic acid that is half of the U.S. permissible exposure limit used for chronic exposure in the workplace.

We wish to report on our company's experience with acrylic acid in an effort to contribute human data to the scientific information the committee uses to establish AEGL values. We believe this data demonstrates that the proposed AEGL-1 value of 1ppm is too low.

Rohm and Haas Company is a global specialty chemical company based in Philadelphia; we have approximately 20,000 employees. Acrylic acid is used at 30 of our plants worldwide as either a raw material or finished product. Our workplace exposure limit is 2ppm 8 hr TWA, with a STEL of 6ppm. We reviewed our U.S. workplace injury and illness reports from 1990, and our worldwide workplace injury and illness reports from 1994 (total of 12,774 records) and found four reports of respiratory or eye irritation involving monomer. In 1994, three employees complained of respiratory irritation after cleaning up a spill of glacial acrylic acid at a railcar loading station. Two employees required first aid, and the third required no treatment. These employees did not require

time off work or medical treatment after the initial first aid. These employees were not wearing personal protective equipment. Air monitoring was not conducted at the time of the spill, but it is reasonable to assume the exposures were substantially higher than our workplace exposure limit. A fourth report involves a release of an inhibitor during tank car loading; the inhibitor was 88% acrylic acid by weight. An employee involved in the release complained of burning eyes. No treatment was required. Again, there was no air monitoring done. However, we believe the small number of cases of respiratory or eye irritation we have experienced despite the large number of employees regularly using acrylic acid around the world are indicative of the safety afforded by the current workplace exposure limit of 2ppm. Additionally, we have no reports of chronic illness due to acrylic acid.

Lastly, we reviewed the health effect allegations reports we maintain for Toxic Substances Control Act reporting purposes. These reports are generated from customer and neighbor calls to the company within the U.S., as well as employee allegations from any plant worldwide. Reviewing these records back to 1983 reveals one incident involving an employee of our customer who was handling acrylic acid and experienced chest pain, leg tingling, and respiratory irritation. Symptoms resolved overnight without treatment. There are no other reports involving acrylic acid.

Sincerely,

Eileen M. Bonner, M.D., M.P.H.
Corporate Medical Director
Rohm and Haas Company

EMB/tt

BASF Corporation

BASF

May 30, 2001

Clay Frederick, Ph.D.
Rohm and Haas Co.
Toxicology Department
727 Norristown Rd.
Spring House, PA 19477

Dear Dr. Frederick,

As per your request, here is a summary of BASF Freeport acrylic acid employee medical surveillance information and workplace air monitoring data for acrylic acid, for use in the BAMM written submission regarding the proposed AEGL values.

Health surveillance and workplace air monitoring data for one producer's acrylic acid plant employees from 1998 to present were reviewed. For the symptoms of concern, odor perception and nasal irritation, limited data were available.

The producer's medical surveillance program does inquire about ear, nose and throat symptoms, but not about odor perception. The producer's medical surveillance program includes a question, "do you have ear, nose or throat trouble?" Nine of 104 employees of the acrylic acid plants evaluated during this period responded affirmatively to this question. Their responses were reviewed, and did not include any specific symptoms of nasal irritation. The reasons for affirmative answer were hayfever, allergies, throat infection, ear infection and sinus infection. All of the employees worked in jobs where they were exposed to acrylic acid below the ACGIH 8 – hour TWA of 2 ppm, as per the producer's industrial hygiene data.

A review of incident reports, injury and illness reports, and first aid reports from 1998 to present demonstrated that there were no employee reports of adverse effects or odor complaints from exposure to acrylic acid vapor. There was one first aid report of redness and irritation from direct contact with acrylic acid liquid mist when a pump seal ruptured and sprayed acrylic acid on employee's face. There were no TSCA 8c reports for acrylic acid.

The BASF Corporate Medical Department would be interested in any additional information from other acrylic acid producers, similar to that we have provided above.

Sincerely,

Julia E. Klees, M.D., M.P.H.
Associate Corporate Medical Director

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
1	CODE 1	CODE 2	PERSONAL (P) OR AREA (A) MONITORING	<	VALUE FOUND	WEL	% OF WEL	WEL TYPE	STANDARD DATE FOR WEL AT THE TIME
2	HTGA	5	A		26	1.0	2600.00%	TWA	19920901
3	008D	831	A		4.27	2.0	213.50%	TWA	19800630
4	801D	3	P		3.7	2.0	185.00%	TWA	19800630
5	DRFA	5	P	<	3.25	1.0	325.00%	TWA	19920901
6	HTMA	5	P		2.6	1.0	260.00%	TWA	19920901
7	HT2A	5	P		2.6	1.0	260.00%	TWA	19920901
8	801D	3	P		2.4	2.0	120.00%	TWA	19800630
9	804D	3	P	<	2.3	2.0	115.00%	TWA	19800630
10	804D	3	P	<	2	2.0	100.00%	TWA	19800630
11	HTMA	5	P	>	1.7	1.0	170.00%	TWA	19920901
12	801B	3	P	<	1.5	2.0	75.00%	TWA	19800630
13	804D	3	P	<	1.5	2.0	75.00%	TWA	19800630
14	HTMA	5	P	>	1.5	1.0	150.00%	TWA	19920901
15	HTEA	5	P		1.4	2.0	70.00%	TWA	19981015
16	017K	632	P		1.2	2.0	60.00%	TWA	19800630
17	028A	3	P	<	1.1	2.0	55.00%	TWA	19800630
18	HT2A	5	P		1.1	1.0	110.00%	TWA	19920901
19	HT2A	5	A		1.1	1.0	110.00%	TWA	19920901
20	010A	632	P		1.06	2.0	53.00%	TWA	19800630
21	017H	632	P		1.01	2.0	50.50%	TWA	19800630
22	HTSA	5	P		1	2.0	50.00%	TWA	19981015
23	HTSA	5	P		1	2.0	50.00%	TWA	19981015
24	HT2A	5	P		0.93	1.0	93.00%	TWA	19920901
25	HT2A	5	P		0.91	1.0	91.00%	TWA	19920901
26	HT2A	5	P		0.91	1.0	91.00%	TWA	19920901
27	801D	3	P	<	0.9	2.0	45.00%	TWA	19800630
28	804D	3	P	<	0.9	2.0	45.00%	TWA	19800630
29	804D	3	P	<	0.9	2.0	45.00%	TWA	19800630
30	HT2M	5	P		0.9	1.0	90.00%	TWA	19920901
31	017H	632	P		0.87	2.0	43.50%	TWA	19800630
32	017B	632	P		0.87	2.0	43.50%	TWA	19800630
33	8WH2	3	P	<	0.8	2.0	40.00%	TWA	19800630
34	801B	3	P	<	0.8	2.0	40.00%	TWA	19800630
35	804D	3	P	<	0.8	2.0	40.00%	TWA	19800630
36	HTGA	5	P		0.79	1.0	79.00%	TWA	19920901
37	017K	632	P		0.74	2.0	37.00%	TWA	19800630
38	804D	3	P	<	0.7	2.0	35.00%	TWA	19800630
39	804D	3	P	<	0.7	2.0	35.00%	TWA	19800630
40	RHTA	5	P		0.7	2.0	35.00%	TWA	19800630
41	HT2A	5	P		0.7	1.0	70.00%	TWA	19920901
42	801D	3	P	<	0.6	2.0	30.00%	TWA	19800630
43	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
44	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
45	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
46	017H	632	P		0.6	2.0	30.00%	TWA	19800630
47	008D	831	A	<	0.6	2.0	30.00%	TWA	19800630
48	005A	5	P		0.59	2.0	29.50%	TWA	19981015

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
49	HTEA	5	P		0.59	1.0	59.00%	TWA	19920901
50	HTSA	5	P		0.58	1.0	58.00%	TWA	19920901
51	HT2A	5	P		0.58	1.0	58.00%	TWA	19920901
52	PH1A	5	P		0.55	2.0	27.50%	TWA	19981015
53	HTGA	5	P		0.55	2.0	27.50%	TWA	19981015
54	HT2A	5	P		0.53	1.0	53.00%	TWA	19920901
55	PH1A	5	P		0.52	2.0	26.00%	TWA	19981015
56	HT2A	5	P		0.52	1.0	52.00%	TWA	19920901
57	HT2A	5	P		0.52	1.0	52.00%	TWA	19920901
58	DRFA	5	P		0.5	1.0	50.00%	TWA	19920901
59	RB3A	5	P		0.46	1.0	46.00%	TWA	19920901
60	HT2M	5	P		0.45	1.0	45.00%	TWA	19920901
61	HTMA	5	P		0.44	2.0	22.00%	TWA	19981015
62	DRFA	5	P		0.43	1.0	43.00%	TWA	19920901
63	DRFA	5	P		0.43	1.0	43.00%	TWA	19920901
64	HT2A	5	P		0.43	1.0	43.00%	TWA	19920901
65	HT2M	5	P		0.42	2.0	21.00%	TWA	19981015
66	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
67	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
68	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
69	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
70	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
71	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
72	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
73	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
74	HT2A	5	P		0.4	1.0	40.00%	TWA	19920901
75	HT2A	5	P	<	0.39	1.0	39.00%	TWA	19920901
76	HTXA	5	P		0.38	1.0	38.00%	TWA	19920901
77	HT2A	5	P		0.37	2.0	18.50%	TWA	19800630
78	HTXA	5	P		0.33	1.0	33.00%	TWA	19920901
79	HTXA	5	P		0.33	1.0	33.00%	TWA	19920901
80	005A	5	P		0.31	2.0	15.50%	TWA	19981015
81	017H	632	P		0.31	2.0	15.50%	TWA	19800630
82	HTEA	5	P		0.3	2.0	15.00%	TWA	19800630
83	HTSA	5	P		0.3	2.0	15.00%	TWA	19981015
84	008D	831	A	<	0.3	2.0	15.00%	TWA	19800630
85	DRFA	5	P		0.29	1.0	29.00%	TWA	19920901
86	HTSA	5	P		0.29	1.0	29.00%	TWA	19920901
87	DRFA	5	P		0.28	2.0	14.00%	TWA	19981015
88	DRFA	5	P		0.28	2.0	14.00%	TWA	19981015
89	RB3A	5	P		0.27	2.0	13.50%	TWA	19981015
90	HTSA	5	P		0.26	2.0	13.00%	TWA	19981015
91	HT2A	5	P		0.26	1.0	26.00%	TWA	19920901
92	HTSA	5	P	<	0.25	1.0	25.00%	TWA	19920901
93	PH1A	5	P		0.24	2.0	12.00%	TWA	19981015
94	HTGA	5	P		0.24	2.0	12.00%	TWA	19981015
95	HTSA	5	P	<	0.24	1.0	24.00%	TWA	19920901
96	017K	632	P		0.24	2.0	12.00%	TWA	19800630
97	PH1A	5	P		0.23	2.0	11.50%	TWA	19981015
98	HTMA	5	P	<	0.23	1.0	23.00%	TWA	19920901
99	HTEA	5	P		0.23	1.0	23.00%	TWA	19920901

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
100	HT2M	5	P		0.23	1.0	23.00%	TWA	19920901
101	HTXA	5	P	<	0.23	1.0	23.00%	TWA	19920901
102	HTEA	5	P	<	0.23	1.0	23.00%	TWA	19920901
103	HTMA	5	P		0.23	1.0	23.00%	TWA	19920901
104	HTGA	5	P	<	0.22	1.0	22.00%	TWA	19920901
105	HTEA	5	P		0.21	2.0	10.50%	TWA	19981015
106	RHTA	5	P		0.21	1.0	21.00%	TWA	19920901
107	HTEA	5	P	<	0.21	1.0	21.00%	TWA	19920901
108	028A	3	A		0.2	2.0	10.00%	TWA	19800630
109	RHTA	5	P		0.2	2.0	10.00%	TWA	19800630
110	HTEA	5	P		0.2	2.0	10.00%	TWA	19800630
111	PH1A	5	P		0.2	2.0	10.00%	TWA	19981015
112	PH1A	5	P		0.2	2.0	10.00%	TWA	19981015
113	HT2M	5	P		0.2	1.0	20.00%	TWA	19920901
114	HTGA	5	P		0.2	1.0	20.00%	TWA	19920901
115	010A	632	P		0.2	2.0	10.00%	TWA	19800630
116	017K	632	P	<	0.2	1.0	20.00%	TWA	19920901
117	HTEA	5	P	<	0.19	1.0	19.00%	TWA	19920901
118	HTXA	5	P	<	0.19	1.0	19.00%	TWA	19920901
119	HTXA	5	P	<	0.19	1.0	19.00%	TWA	19920901
120	HTSA	5	P		0.18	1.0	18.00%	TWA	19920901
121	HTSA	5	P		0.18	1.0	18.00%	TWA	19920901
122	HTEA	5	P		0.18	1.0	18.00%	TWA	19920901
123	007E	751	P		0.18	2.0	9.00%	TWA	19800630
124	HTMA	5	P		0.17	1.0	17.00%	TWA	19920901
125	HT2M	5	P		0.17	1.0	17.00%	TWA	19920901
126	HTEA	5	P		0.17	1.0	17.00%	TWA	19920901
127	PH1A	5	P		0.16	2.0	8.00%	TWA	19981015
128	HTSA	5	P		0.16	1.0	16.00%	TWA	19920901
129	005A	5	P		0.15	2.0	7.50%	TWA	19981015
130	HTGA	5	P		0.15	1.0	15.00%	TWA	19920901
131	HTSA	5	P		0.15	1.0	15.00%	TWA	19920901
132	TRAK	5	P		0.14	2.0	7.00%	TWA	19981015
133	HTEA	5	P		0.14	1.0	14.00%	TWA	19920901
134	HT2A	5	P		0.14	1.0	14.00%	TWA	19920901
135	HTSA	5	P		0.14	1.0	14.00%	TWA	19920901
136	RHTA	5	P		0.13	1.0	13.00%	TWA	19920901
137	HT2A	5	P		0.12	1.0	12.00%	TWA	19920901
138	HTEA	5	P		0.11	1.0	11.00%	TWA	19920901
139	HTEA	5	P		0.11	1.0	11.00%	TWA	19920901
140	HTXA	5	P	<	0.11	1.0	11.00%	TWA	19920901
141	HTGA	5	P	<	0.11	1.0	11.00%	TWA	19920901
142	017K	632	P		0.11	2.0	5.50%	TWA	19800630
143	028A	3	P	<	0.1	2.0	5.00%	TWA	19800630
144	HTEA	5	P		0.1	2.0	5.00%	TWA	19800630
145	HTGA	5	P		0.1	2.0	5.00%	TWA	19981015
146	RHTA	5	P		0.1	1.0	10.00%	TWA	19920901
147	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901
148	HTEA	5	P		0.1	1.0	10.00%	TWA	19920901
149	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901
150	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
151	600B	611	A	<	0.1	5.0	2.00%	TWA	19780926
152	017K	632	P	<	0.1	2.0	5.00%	TWA	19800630
153	002F	632	P	<	0.1	2.0	5.00%	TWA	19800630
154	017B	632	P	<	0.1	1.0	10.00%	TWA	19920901
155	PH1A	5	P		0.098	2.0	4.90%	TWA	19981015
156	HTSA	5	P		0.096	1.0	9.60%	TWA	19920901
157	DRFA	5	P		0.094	1.0	9.40%	TWA	19920901
158	HTMA	5	P		0.091	2.0	4.60%	TWA	19981015
159	PDLA	5	P		0.09	2.0	4.50%	TWA	19800630
160	HT2A	5	P		0.09	2.0	4.50%	TWA	19981015
161	017B	632	P		0.09	1.0	9.00%	TWA	19920901
162	008D	831	A		0.09	2.0	4.50%	TWA	19800630
163	017D	632	P		0.086	2.0	4.30%	TWA	19981015
164	HT2A	5	P		0.085	1.0	8.50%	TWA	19920901
165	002B	396	A	<	0.081	1.0	8.10%	TWA	19920901
166	008D	831	A		0.0752	2.0	3.80%	TWA	19800630
167	RHTA	5	P		0.073	1.0	7.30%	TWA	19920901
168	HTEA	5	P		0.072	1.0	7.20%	TWA	19920901
169	HT2M	5	P		0.068	1.0	6.80%	TWA	19920901
170	DRFA	5	P		0.067	1.0	6.70%	TWA	19920901
171	005A	5	P		0.063	2.0	3.20%	TWA	19981015
172	HTEA	5	P		0.062	2.0	3.10%	TWA	19981015
173	HT2A	5	P		0.062	1.0	6.20%	TWA	19920901
174	HT2M	5	A		0.06	1.0	6.00%	TWA	19920901
175	005A	808	A		0.06	2.0	3.00%	TWA	19981015
176	HTSA	5	P		0.058	1.0	5.80%	TWA	19920901
177	HTEA	5	P	<	0.058	1.0	5.80%	TWA	19920901
178	HT2A	5	P	<	0.057	1.0	5.70%	TWA	19920901
179	HT2A	5	P	<	0.057	1.0	5.70%	TWA	19920901
180	HT2A	5	A		0.057	1.0	5.70%	TWA	19920901
181	HTSA	5	P		0.056	2.0	2.80%	TWA	19981015
182	HT2A	5	P		0.056	1.0	5.60%	TWA	19920901
183	HTEA	5	P		0.055	2.0	2.80%	TWA	19981015
184	HTMA	5	P		0.054	2.0	2.70%	TWA	19981015
185	HTXA	5	P		0.052	1.0	5.20%	TWA	19920901
186	HTEA	5	P		0.05	2.0	2.50%	TWA	19800630
187	HT2A	5	P		0.05	1.0	5.00%	TWA	19920901
188	HTEA	5	P	<	0.049	1.0	4.90%	TWA	19920901
189	HTXA	5	P		0.048	1.0	4.80%	TWA	19920901
190	HTEA	5	P	<	0.047	1.0	4.70%	TWA	19920901
191	HTXA	5	P		0.047	1.0	4.70%	TWA	19920901
192	HT2A	5	P		0.047	1.0	4.70%	TWA	19920901
193	HTXA	5	P	<	0.046	1.0	4.60%	TWA	19920901
194	HTXA	5	P	<	0.046	1.0	4.60%	TWA	19920901
195	HTXA	5	P		0.046	1.0	4.60%	TWA	19920901
196	HTEA	5	A	<	0.046	1.0	4.60%	TWA	19920901
197	HTXA	5	A	<	0.046	1.0	4.60%	TWA	19920901
198	HTEA	5	P	<	0.045	1.0	4.50%	TWA	19920901
199	HTXA	5	P	<	0.045	1.0	4.50%	TWA	19920901
200	HTXA	5	P	<	0.045	1.0	4.50%	TWA	19920901
201	HTSA	5	A	<	0.045	1.0	4.50%	TWA	19920901

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
202	HTEA	5	P		0.044	2.0	2.20%	TWA	19981015
203	HTEA	5	P	<	0.044	1.0	4.40%	TWA	19920901
204	HTEA	5	P		0.044	1.0	4.40%	TWA	19920901
205	HTXA	5	P		0.042	2.0	2.10%	TWA	19981015
206	HTXA	5	A	<	0.042	1.0	4.20%	TWA	19920901
207	03AC	9	A	<	0.04	2.0	2.00%	TWA	19981015
208	RHTA	5	P		0.039	1.0	3.90%	TWA	19920901
209	HT2A	5	P		0.038	2.0	1.90%	TWA	19981015
210	HTEA	5	P	<	0.038	1.0	3.80%	TWA	19920901
211	HT2A	5	P		0.037	2.0	1.90%	TWA	19981015
212	HT2A	5	P		0.037	2.0	1.90%	TWA	19981015
213	HTEA	5	A	<	0.037	1.0	3.70%	TWA	19920901
214	HTSA	5	P		0.035	1.0	3.50%	TWA	19920901
215	HT2A	5	P		0.033	2.0	1.70%	TWA	19981015
216	03AC	9	A	<	0.033	2.0	1.70%	TWA	19981015
217	03AC	9	A	<	0.033	2.0	1.70%	TWA	19981015
218	HTGA	5	P	<	0.031	2.0	1.60%	TWA	19981015
219	HTGA	5	P	<	0.031	2.0	1.60%	TWA	19981015
220	DPAA	5	P	<	0.031	2.0	1.60%	TWA	19981015
221	64BD	3	P	<	0.03	2.0	1.50%	TWA	19800630
222	017K	632	A		0.03	2.0	1.50%	TWA	19800630
223	081A	751	P	<	0.03	1.0	3.00%	TWA	19920901
224	081A	751	P	<	0.03	1.0	3.00%	TWA	19920901
225	PH1A	5	P	<	0.029	2.0	1.50%	TWA	19981015
226	HTSA	5	P		0.029	2.0	1.50%	TWA	19981015
227	HT2A	5	P	<	0.029	2.0	1.50%	TWA	19981015
228	HT2A	5	P	<	0.028	2.0	1.40%	TWA	19981015
229	005A	5	P	<	0.025	2.0	1.30%	TWA	19981015
230	HT2A	5	P	<	0.025	2.0	1.30%	TWA	19981015
231	HT2A	5	P	<	0.022	2.0	1.10%	TWA	19981015
232	HTXA	5	P	<	0.021	2.0	1.10%	TWA	19981015
233	HTXA	5	P	<	0.021	1.0	2.10%	TWA	19920901
234	HTEA	5	P	<	0.021	1.0	2.10%	TWA	19920901
235	HTXA	5	P	<	0.02	2.0	1.00%	TWA	19981015
236	HTXA	5	P	<	0.02	2.0	1.00%	TWA	19981015
237	HT2A	5	P	<	0.02	2.0	1.00%	TWA	19981015
238	002B	396	A		0.02	1.0	2.00%	TWA	19920901
239	017K	632	P	<	0.02	2.0	1.00%	TWA	19800630
240	017B	632	P	<	0.02	2.0	1.00%	TWA	19800630
241	002C	632	P		0.02	2.0	1.00%	TWA	19800630
242	017K	632	A	<	0.02	2.0	1.00%	TWA	19800630
243	HT2A	5	P		0.018	1.0	1.80%	TWA	19920901
244	005A	808	A		0.018	2.0	0.90%	TWA	19981015
245	03AC	9	A		0.017	2.0	0.90%	TWA	19981015
246	001E	319	A	<	0.016	2.0	0.80%	TWA	19800630
247	HTXA	5	P		0.014	1.0	1.40%	TWA	19920901
248	002C	396	A	<	0.014	1.0	1.40%	TWA	19920901
249	017B	632	P		0.012	1.0	1.20%	TWA	19920901
250	HT2A	5	P	<	0.01	2.0	0.50%	TWA	19981015
251	HT2A	5	P		0.01	1.0	1.00%	TWA	19920901
252	017B	632	P	<	0.01	2.0	0.50%	TWA	19800630

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Acrylic Acid Data Summary (1980 to Present)

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	A	B	C	D	E	F	G	H	I
253	017K	632	P	<	0.01	2.0	0.50%	TWA	19800630
254	017K	632	P	<	0.01	2.0	0.50%	TWA	19800630
255	002C	632	P	<	0.01	2.0	0.50%	TWA	19800630
256	HT2M	5	P	<	0.0066	2.0	0.30%	TWA	19981015
257	HT2M	5	P		0.0065	2.0	0.30%	TWA	19981015
258	HT2A	5	P		0.0063	2.0	0.30%	TWA	19981015
259	017K	632	P		0.003	1.0	0.30%	TWA	19920901
260	HT2A	5	P		0.0028	1.0	0.30%	TWA	19920901
261			Average =		0.3513 (Does not include 26 ppm value as outlier)				
262			Geometric Mean =		0.1375 (Does not include 26 ppm value as outlier)				
263			Median =		0.15				
264	22 values of 1 ppm or over for 8% of total (Includes limit of detection samples)								
265	9 values of 2 ppm or over for 3% of total (Includes limit of detection samples)								
266	Range = 0.003 (or nondetect at the limit of detection of the analytical method								
267	used at the time) to 4.3 ppm excluding the single 26 ppm outlier								

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Acrylic Acid Data Summary (1980 to Present)

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	A	B	C	D	E	F	G	H	I
1	CODE 1	CODE 2	PERSONAL (P) OR AREA (A) MONITORING	<	VALUE FOUND	WEL	% OF WEL	WEL TYPE	STANDARD DATE FOR WEL AT THE TIME
2	003C	16	P		63	5.0	1260.00%	STEL	19800630
3	009C	15	P		62.4	3.0	2080.00%	STEL	19920901
4	ELYA	4	A		57	5.0	1140.00%	STEL	19800630
5	WTFA	4	A		48	3.0	1600.00%	STEL	19920901
6	WTFA	4	P		32	3.0	1066.70%	STEL	19920901
7	002A	912	P	<	30	5.0	600.00%	STEL	19800630
8	RHTA	5	P		24	5.0	480.00%	STEL	19800630
9	ETFA	4	P		23	5.0	460.00%	STEL	19800630
10	HTSA	5	P		23	15.0	153.30%	STEL	19780417
11	HTEA	5	P		18	3.0	600.00%	STEL	19920901
12	008D	831	A	<	15	5.0	300.00%	STEL	19800630
13	046D	751	P		14.8	5.0	296.00%	STEL	19800630
14	001E	319	P		13.8	5.0	276.00%	STEL	19800630
15	028A	3	P		11.6	5.0	232.00%	STEL	19800630
16	046D	751	P		11.4	5.0	228.00%	STEL	19800630
17	030B	3	A		10.8	5.0	216.00%	STEL	19800630
18	015A	735	P		10.1	5.0	202.00%	STEL	19800630
19	RHTA	5	P		9.8	5.0	196.00%	STEL	19800630
20	HTEA	5	P		9.8	3.0	326.70%	STEL	19920901
21	HTMA	5	P		9.4	15.0	62.70%	STEL	19780417
22	ETFA	4	A		9	5.0	180.00%	STEL	19800630
23	HTSA	5	P		8.9	5.0	178.00%	STEL	19800630
24	ETFA	4	P		8.4	5.0	168.00%	STEL	19800630
25	ETFA	4	P		8.3	5.0	166.00%	STEL	19800630
26	028A	3	P	<	7.9	5.0	158.00%	STEL	19800630
27	039D	3	P		7.8	5.0	156.00%	STEL	19800630
28	031C	2	P		7	15.0	46.70%	STEL	19780417
29	046D	751	P		7	5.0	140.00%	STEL	19800630
30	015A	735	P		6.9	5.0	138.00%	STEL	19800630
31	001E	735	P		6.8	5.0	136.00%	STEL	19800630
32	046D	751	P		6.6	5.0	132.00%	STEL	19800630
33	ETFA	4	P		6.5	5.0	130.00%	STEL	19800630
34	008D	831	A		6.4	5.0	128.00%	STEL	19800630
35	028A	3	P		6.2	5.0	124.00%	STEL	19800630
36	004A	912	P	<	6	5.0	120.00%	STEL	19800630
37	001C	4	P		5.9	5.0	118.00%	STEL	19800630
38	HTMA	5	A		5.9	3.0	196.70%	STEL	19920901
39	028A	3	P		5.77	5.0	115.40%	STEL	19800630
40	WTFA	4	A		5.7	5.0	114.00%	STEL	19800630
41	046B	751	A		5.5	3.0	183.30%	STEL	19920901
42	030B	3	A		5.4	5.0	108.00%	STEL	19800630
43	HTSA	5	P		5.2	15.0	34.70%	STEL	19780417
44	HT2M	5	P		5.2	3.0	173.30%	STEL	19920901
45	801D	3	P		5	5.0	100.00%	STEL	19800630
46	003C	16	P	<	5	5.0	100.00%	STEL	19800630
47	001D	16	P	<	5	3.0	166.70%	STEL	19920901
48	ETFA	4	P		4.9	3.0	163.30%	STEL	19920901

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
49	008D	831	A		4.9	5.0	98.00%	STEL	19800630
50	HT2M	5	A		4.8	3.0	160.00%	STEL	19920901
51	ETFA	4	P		4.76	5.0	95.20%	STEL	19800630
52	ETFA	4	P		4.6	5.0	92.00%	STEL	19800630
53	HTMA	5	A		4.6	3.0	153.30%	STEL	19920901
54	ETFA	4	P		4.5	5.0	90.00%	STEL	19800630
55	ELYA	4	A		4.5	5.0	90.00%	STEL	19800630
56	HTMA	5	P		4.5	5.0	90.00%	STEL	19800630
57	006A	319	A		4.48	5.0	89.60%	STEL	19800630
58	BDSA	3	P	<	4.3	5.0	86.00%	STEL	19800630
59	BDSA	3	P	<	4.2	5.0	84.00%	STEL	19800630
60	WTFA	4	P	<	4	5.0	80.00%	STEL	19800630
61	HTMA	5	P		4	3.0	133.30%	STEL	19920901
62	003C	16	P	<	4	5.0	80.00%	STEL	19800630
63	001B	735	P	<	4	5.0	80.00%	STEL	19800630
64	015A	735	P		4	5.0	80.00%	STEL	19800630
65	HT2M	5	A		3.95	3.0	131.70%	STEL	19920901
66	030C	3	P		3.9	5.0	78.00%	STEL	19800630
67	01AA	4	P	<	3.81	5.0	76.20%	STEL	19800630
68	001E	319	P		3.78	5.0	75.60%	STEL	19800630
69	001B	319	P		3.78	5.0	75.60%	STEL	19800630
70	HT2A	5	P	<	3.7	5.0	74.00%	STEL	19800630
71	ETFA	4	P		3.6	6.0	60.00%	STEL	19981015
72	009C	15	P		3.6	3.0	120.00%	STEL	19920901
73	028A	3	P	<	3.5	5.0	70.00%	STEL	19800630
74	030F	3	P		3.5	5.0	70.00%	STEL	19800630
75	014G	7	P	<	3.5	6.0	58.30%	STEL	19981015
76	007E	751	P		3.5	5.0	70.00%	STEL	19800630
77	ETFA	4	P		3.41	5.0	68.20%	STEL	19800630
78	030F	3	P		3.4	5.0	68.00%	STEL	19800630
79	030B	3	P		3.4	5.0	68.00%	STEL	19800630
80	01AA	4	P	<	3.4	5.0	68.00%	STEL	19800630
81	DPAA	5	A		3.2	5.0	64.00%	STEL	19800630
82	134B	3	A		3.1	5.0	62.00%	STEL	19800630
83	HTMA	5	A		3.1	3.0	103.30%	STEL	19920901
84	001B	735	P		3.1	5.0	62.00%	STEL	19800630
85	ETFA	4	P		3	5.0	60.00%	STEL	19800630
86	001G	735	P	<	3	5.0	60.00%	STEL	19800630
87	015A	735	P		3	5.0	60.00%	STEL	19800630
88	046B	751	A		3	5.0	60.00%	STEL	19800630
89	R12E	2	P		2.9	5.0	58.00%	STEL	19800630
90	RHTA	5	P		2.9	5.0	58.00%	STEL	19800630
91	100E	641	P		2.9	3.0	96.70%	STEL	19920901
92	134B	3	A	<	2.8	5.0	56.00%	STEL	19800630
93	028A	3	P	<	2.7	5.0	54.00%	STEL	19800630
94	B3AA	5	P	<	2.7	3.0	90.00%	STEL	19920901
95	046B	751	A		2.7	5.0	54.00%	STEL	19800630
96	030F	3	P		2.6	5.0	52.00%	STEL	19800630
97	046B	751	P		2.6	5.0	52.00%	STEL	19800630
98	ETFA	4	P		2.5	6.0	41.70%	STEL	19981015
99	ETFA	4	P	<	2.5	5.0	50.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
100	011F	9	P		2.5	3.0	83.30%	STEL	19920901
101	003C	16	A		2.5	5.0	50.00%	STEL	19800630
102	046B	751	P		2.5	5.0	50.00%	STEL	19800630
103	028A	3	P	<	2.4	15.0	16.00%	STEL	19780417
104	028A	3	P		2.4	5.0	48.00%	STEL	19800630
105	ETFA	4	P		2.4	5.0	48.00%	STEL	19800630
106	007E	751	P	<	2.4	5.0	48.00%	STEL	19800630
107	008D	831	A		2.38	5.0	47.60%	STEL	19800630
108	014G	7	P	<	2.3	6.0	38.30%	STEL	19981015
109	978A	840	P		2.3	3.0	76.70%	STEL	19920901
110	ETFA	4	P	<	2.26	5.0	45.20%	STEL	19800630
111	028A	3	P	<	2.2	15.0	14.70%	STEL	19780417
112	007E	751	P		2.18	5.0	43.60%	STEL	19800630
113	030B	3	A		2.1	5.0	42.00%	STEL	19800630
114	002C	318	P		2.1	3.0	70.00%	STEL	19920901
115	ETFA	4	P		2	5.0	40.00%	STEL	19800630
116	001C	4	P		2	5.0	40.00%	STEL	19800630
117	003C	16	P	<	2	5.0	40.00%	STEL	19800630
118	003C	16	P	<	2	3.0	66.70%	STEL	19920901
119	003C	16	P	<	2	3.0	66.70%	STEL	19920901
120	003C	16	P	<	2	3.0	66.70%	STEL	19920901
121	009A	396	P		2	3.0	66.70%	STEL	19920901
122	009A	396	A	<	2	3.0	66.70%	STEL	19920901
123	009A	396	A	<	2	3.0	66.70%	STEL	19920901
124	005C	399	P	<	2	3.0	66.70%	STEL	19920901
125	002C	681	P	<	2	5.0	40.00%	STEL	19800630
126	001E	735	P	<	2	5.0	40.00%	STEL	19800630
127	YARD	831	P		2	3.0	66.70%	STEL	19920901
128	HTEA	5	P		1.9	3.0	63.30%	STEL	19920901
129	HT2M	5	A		1.9	3.0	63.30%	STEL	19920901
130	001B	319	A		1.84	5.0	36.80%	STEL	19800630
131	ETFA	4	P		1.8	3.0	60.00%	STEL	19920901
132	HTEA	5	P		1.8	15.0	12.00%	STEL	19780417
133	B3AA	5	P	<	1.8	3.0	60.00%	STEL	19920901
134	HT2M	5	P		1.8	3.0	60.00%	STEL	19920901
135	HT2M	5	A		1.8	3.0	60.00%	STEL	19920901
136	WTFA	4	P	<	1.77	5.0	35.40%	STEL	19800630
137	WTFA	4	P	<	1.76	5.0	35.20%	STEL	19800630
138	028A	3	A	<	1.7	5.0	34.00%	STEL	19800630
139	030F	3	A		1.7	5.0	34.00%	STEL	19800630
140	030F	3	A		1.7	5.0	34.00%	STEL	19800630
141	028A	3	A		1.7	3.0	56.70%	STEL	19920901
142	001C	4	P		1.7	5.0	34.00%	STEL	19800630
143	009A	4	A		1.7	3.0	56.70%	STEL	19920901
144	011F	9	P		1.7	3.0	56.70%	STEL	19920901
145	100E	641	P		1.7	5.0	34.00%	STEL	19800630
146	046B	751	P		1.7	3.0	56.70%	STEL	19920901
147	005A	808	P		1.7	3.0	56.70%	STEL	19920901
148	008D	831	A		1.7	5.0	34.00%	STEL	19800630
149	028A	3	P		1.6	5.0	32.00%	STEL	19800630
150	030D	3	P	<	1.6	5.0	32.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
151	001C	4	P		1.6	5.0	32.00%	STEL	19800630
152	HTEA	5	P		1.6	15.0	10.70%	STEL	19780417
153	002C	318	P	<	1.6	3.0	53.30%	STEL	19920901
154	002A	852	P		1.6	3.0	53.30%	STEL	19920901
155	ETFA	4	P		1.54	5.0	30.80%	STEL	19800630
156	WTFA	4	P		1.5	6.0	25.00%	STEL	19981015
157	RHTA	5	P		1.5	5.0	30.00%	STEL	19800630
158	014G	7	P	<	1.5	6.0	25.00%	STEL	19981015
159	009C	15	P		1.5	3.0	50.00%	STEL	19920901
160	ETFA	4	P		1.4	5.0	28.00%	STEL	19800630
161	01AA	4	P	<	1.4	5.0	28.00%	STEL	19800630
162	ETFA	4	A		1.4	6.0	23.30%	STEL	19981015
163	HT2M	5	P		1.4	3.0	46.70%	STEL	19920901
164	060F	711	P	<	1.4	5.0	28.00%	STEL	19800630
165	002A	852	P		1.4	6.0	23.30%	STEL	19981015
166	WTFA	4	P	<	1.3	5.0	26.00%	STEL	19800630
167	003C	16	P		1.3	3.0	43.30%	STEL	19920901
168	003C	16	P		1.3	3.0	43.30%	STEL	19920901
169	046B	751	P	<	1.3	3.0	43.30%	STEL	19920901
170	010L	821	P		1.3	5.0	26.00%	STEL	19800630
171	ETFA	4	P	<	1.26	5.0	25.20%	STEL	19800630
172	501B	222	P		1.25	3.0	41.70%	STEL	19920901
173	64BD	3	P	<	1.23	5.0	24.60%	STEL	19800630
174	01AA	4	P	<	1.21	5.0	24.20%	STEL	19800630
175	028A	3	A	<	1.2	5.0	24.00%	STEL	19800630
176	030F	3	A	<	1.2	5.0	24.00%	STEL	19800630
177	ETFA	4	P		1.2	5.0	24.00%	STEL	19800630
178	01AA	4	P		1.2	3.0	40.00%	STEL	19920901
179	001B	4	A		1.2	3.0	40.00%	STEL	19920901
180	HTEA	5	P		1.2	15.0	8.00%	STEL	19780417
181	HT2M	5	A		1.2	3.0	40.00%	STEL	19920901
182	003C	7	P	<	1.2	6.0	20.00%	STEL	19981015
183	03AC	9	P	<	1.2	6.0	20.00%	STEL	19981015
184	002C	808	P	<	1.2	3.0	40.00%	STEL	19920901
185	RHTA	5	P		1.17	5.0	23.40%	STEL	19800630
186	007E	751	P		1.15	5.0	23.00%	STEL	19800630
187	002C	808	P	<	1.1	3.0	36.70%	STEL	19920901
188	010S	821	P		1.1	3.0	36.70%	STEL	19920901
189	007E	751	P		1.03	5.0	20.60%	STEL	19800630
190	028A	3	P	<	1	5.0	20.00%	STEL	19800630
191	028A	3	P		1	5.0	20.00%	STEL	19800630
192	028A	3	P	<	1	5.0	20.00%	STEL	19800630
193	028A	3	P	<	1	5.0	20.00%	STEL	19800630
194	028A	3	A		1	5.0	20.00%	STEL	19800630
195	016C	4	A	<	1	5.0	20.00%	STEL	19800630
196	001B	4	A	<	1	5.0	20.00%	STEL	19800630
197	RHTA	5	P	<	1	5.0	20.00%	STEL	19800630
198	DRFA	5	P		1	3.0	33.30%	STEL	19920901
199	B3MA	5	P	<	1	3.0	33.30%	STEL	19920901
200	03AC	9	P	<	1	5.0	20.00%	STEL	19800630
201	006D	15	P	<	1	5.0	20.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
202	009A	396	P		1	3.0	33.30%	STEL	19920901
203	002C	396	P	<	1	3.0	33.30%	STEL	19920901
204	001H	399	P	<	1	5.0	20.00%	STEL	19800630
205	005A	681	P	<	1	5.0	20.00%	STEL	19800630
206	002C	681	A	<	1	5.0	20.00%	STEL	19800630
207	002C	681	A	<	1	5.0	20.00%	STEL	19800630
208	005A	808	P		1	3.0	33.30%	STEL	19920901
209	010L	821	P	<	1	5.0	20.00%	STEL	19800630
210	070A	821	A	<	1	5.0	20.00%	STEL	19800630
211	010L	821	A	<	1	5.0	20.00%	STEL	19800630
212	010L	821	A	<	1	5.0	20.00%	STEL	19800630
213	010L	821	A	<	1	5.0	20.00%	STEL	19800630
214	010L	821	A	<	1	5.0	20.00%	STEL	19800630
215	008D	831	A	<	1	5.0	20.00%	STEL	19800630
216	014L	7	P		0.99	6.0	16.50%	STEL	19981015
217	057E	7	P		0.98	3.0	32.70%	STEL	19920901
218	002A	912	P		0.98	3.0	32.70%	STEL	19920901
219	003C	16	P		0.97	3.0	32.30%	STEL	19920901
220	001F	396	P		0.96	3.0	32.00%	STEL	19920901
221	010A	632	P		0.96	5.0	19.20%	STEL	19800630
222	B3AA	5	P	<	0.95	3.0	31.70%	STEL	19920901
223	072C	711	P	<	0.95	5.0	19.00%	STEL	19800630
224	022I	622	A		0.94	5.0	18.80%	STEL	19800630
225	022F	622	A		0.94	5.0	18.80%	STEL	19800630
226	B3AA	5	P	<	0.93	3.0	31.00%	STEL	19920901
227	053A	2	P		0.9	5.0	18.00%	STEL	19800630
228	089B	3	P		0.9	5.0	18.00%	STEL	19800630
229	030F	3	A	<	0.9	5.0	18.00%	STEL	19800630
230	ETFA	4	P	<	0.9	5.0	18.00%	STEL	19800630
231	HTSA	5	P		0.9	15.0	6.00%	STEL	19780417
232	005C	399	P	<	0.9	3.0	30.00%	STEL	19920901
233	001H	399	A		0.9	5.0	18.00%	STEL	19800630
234	057E	7	P		0.89	3.0	29.70%	STEL	19920901
235	022I	622	A		0.89	5.0	17.80%	STEL	19800630
236	022F	622	A		0.88	5.0	17.60%	STEL	19800630
237	022F	622	A		0.88	5.0	17.60%	STEL	19800630
238	072C	711	P	<	0.87	5.0	17.40%	STEL	19800630
239	022F	622	A		0.86	5.0	17.20%	STEL	19800630
240	010A	821	P		0.86	6.0	14.30%	STEL	19981015
241	801D	3	P		0.85	5.0	17.00%	STEL	19800630
242	022I	622	A		0.85	5.0	17.00%	STEL	19800630
243	022I	622	A		0.85	5.0	17.00%	STEL	19800630
244	002C	808	P	<	0.85	3.0	28.30%	STEL	19920901
245	022I	622	A		0.84	5.0	16.80%	STEL	19800630
246	022I	622	A		0.83	5.0	16.60%	STEL	19800630
247	001D	16	P		0.82	6.0	13.70%	STEL	19981015
248	022I	622	A		0.82	5.0	16.40%	STEL	19800630
249	017L	651	P		0.82	6.0	13.70%	STEL	19981015
250	WTFA	4	P		0.8	3.0	26.70%	STEL	19920901
251	WTFA	4	A	<	0.8	5.0	16.00%	STEL	19800630
252	006A	319	P		0.8	5.0	16.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

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	A	B	C	D	E	F	G	H	I
253	005C	399	P	<	0.8	3.0	26.70%	STEL	19920901
254	017K	632	A		0.79	5.0	15.80%	STEL	19800630
255	978D	840	A		0.79	6.0	13.20%	STEL	19981015
256	009A	4	P		0.78	6.0	13.00%	STEL	19981015
257	048A	632	P		0.78	5.0	15.60%	STEL	19800630
258	046B	751	P		0.78	3.0	26.00%	STEL	19920901
259	001B	4	A	<	0.77	3.0	25.70%	STEL	19920901
260	008D	831	P		0.77	6.0	12.80%	STEL	19981015
261	022I	622	A		0.76	5.0	15.20%	STEL	19800630
262	ETFA	4	P	<	0.75	5.0	15.00%	STEL	19800630
263	001C	4	P		0.75	3.0	25.00%	STEL	19920901
264	014L	7	P		0.74	6.0	12.30%	STEL	19981015
265	072C	711	P	<	0.74	5.0	14.80%	STEL	19800630
266	003C	16	P		0.73	6.0	12.20%	STEL	19981015
267	003C	16	P		0.73	3.0	24.30%	STEL	19920901
268	028A	3	P		0.71	5.0	14.20%	STEL	19800630
269	01AA	4	P	<	0.7	5.0	14.00%	STEL	19800630
270	01AA	4	P		0.7	3.0	23.30%	STEL	19920901
271	HTEA	5	P		0.7	15.0	4.70%	STEL	19780417
272	RHTA	5	P		0.7	5.0	14.00%	STEL	19800630
273	001H	399	A	<	0.7	5.0	14.00%	STEL	19800630
274	017K	632	A		0.69	5.0	13.80%	STEL	19800630
275	028A	3	P		0.66	5.0	13.20%	STEL	19800630
276	014L	7	P	<	0.65	6.0	10.80%	STEL	19981015
277	004A	912	P	<	0.65	5.0	13.00%	STEL	19800630
278	003C	16	P		0.64	3.0	21.30%	STEL	19920901
279	B3AA	5	A	<	0.63	3.0	21.00%	STEL	19920901
280	057E	7	A		0.63	3.0	21.00%	STEL	19920901
281	010F	735	P	<	0.63	3.0	21.00%	STEL	19920901
282	005A	808	P		0.63	3.0	21.00%	STEL	19920901
283	ETFA	4	P		0.62	5.0	12.40%	STEL	19800630
284	WTFA	4	P		0.62	5.0	12.40%	STEL	19800630
285	004A	8	P		0.62	6.0	10.30%	STEL	19981015
286	003C	16	P		0.62	6.0	10.30%	STEL	19981015
287	003C	16	P		0.61	3.0	20.30%	STEL	19920901
288	ETFA	4	P	<	0.6	5.0	12.00%	STEL	19800630
289	ETFA	4	P	<	0.6	5.0	12.00%	STEL	19800630
290	ETFA	4	P		0.6	3.0	20.00%	STEL	19920901
291	ETFA	4	P	<	0.6	3.0	20.00%	STEL	19920901
292	WTFA	4	P	<	0.6	3.0	20.00%	STEL	19920901
293	HTSA	5	P		0.6	15.0	4.00%	STEL	19780417
294	PDLA	5	P		0.6	5.0	12.00%	STEL	19800630
295	HTEA	5	P	<	0.6	3.0	20.00%	STEL	19920901
296	03AB	9	P	<	0.6	3.0	20.00%	STEL	19920901
297	006D	15	P		0.6	5.0	12.00%	STEL	19800630
298	003C	16	P		0.6	3.0	20.00%	STEL	19920901
299	048A	632	P		0.6	5.0	12.00%	STEL	19800630
300	017L	651	P		0.59	6.0	9.80%	STEL	19981015
301	028A	3	A		0.58	5.0	11.60%	STEL	19800630
302	057A	7	P		0.58	3.0	19.30%	STEL	19920901
303	001B	319	A		0.58	5.0	11.60%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
304	010S	821	P		0.58	3.0	19.30%	STEL	19920901
305	009C	15	P		0.57	3.0	19.00%	STEL	19920901
306	072C	711	P		0.57	6.0	9.50%	STEL	19981015
307	010S	821	P		0.56	5.0	11.20%	STEL	19800630
308	978D	840	A	<	0.55	6.0	9.20%	STEL	19981015
309	01AA	4	P	<	0.54	5.0	10.80%	STEL	19800630
310	001D	16	P	<	0.54	3.0	18.00%	STEL	19920901
311	978D	840	A	<	0.54	6.0	9.00%	STEL	19981015
312	004C	889	P	<	0.54	3.0	18.00%	STEL	19920901
313	HTSA	5	P		0.52	6.0	8.70%	STEL	19981015
314	003C	16	P		0.52	6.0	8.70%	STEL	19981015
315	003C	16	P		0.52	3.0	17.30%	STEL	19920901
316	028A	3	A		0.51	5.0	10.20%	STEL	19800630
317	134B	3	A	<	0.5	5.0	10.00%	STEL	19800630
318	01AA	4	P	<	0.5	5.0	10.00%	STEL	19800630
319	01AA	4	P	<	0.5	5.0	10.00%	STEL	19800630
320	ETFA	4	P	<	0.5	3.0	16.70%	STEL	19920901
321	009A	4	P		0.5	3.0	16.70%	STEL	19920901
322	01AA	4	P	<	0.5	3.0	16.70%	STEL	19920901
323	01AA	4	P	<	0.5	3.0	16.70%	STEL	19920901
324	072C	711	P	<	0.5	5.0	10.00%	STEL	19800630
325	010F	735	P	<	0.5	5.0	10.00%	STEL	19800630
326	008D	831	A	<	0.5	5.0	10.00%	STEL	19800630
327	008D	831	A		0.5	5.0	10.00%	STEL	19800630
328	ETFA	4	P		0.49	6.0	8.20%	STEL	19981015
329	WTFA	4	P		0.49	5.0	9.80%	STEL	19800630
330	001C	4	P		0.49	3.0	16.30%	STEL	19920901
331	017H	632	A		0.49	5.0	9.80%	STEL	19800630
332	072A	711	P		0.48	5.0	9.60%	STEL	19800630
333	072C	711	P		0.47	6.0	7.80%	STEL	19981015
334	WTFA	4	P		0.44	5.0	8.80%	STEL	19800630
335	ETFA	4	P		0.44	3.0	14.70%	STEL	19920901
336	003C	16	P		0.44	3.0	14.70%	STEL	19920901
337	014G	7	P	<	0.43	6.0	7.20%	STEL	19981015
338	001D	16	P	<	0.43	3.0	14.30%	STEL	19920901
339	501B	222	P	<	0.43	3.0	14.30%	STEL	19920901
340	072C	711	A		0.43	6.0	7.20%	STEL	19981015
341	005A	808	P		0.43	3.0	14.30%	STEL	19920901
342	001D	16	P		0.42	3.0	14.00%	STEL	19920901
343	001D	16	P		0.42	3.0	14.00%	STEL	19920901
344	031A	2	P		0.41	15.0	2.70%	STEL	19780417
345	HT2M	5	P		0.405	3.0	13.50%	STEL	19920901
346	137A	3	P	<	0.4	6.0	6.70%	STEL	19981015
347	007A	3	P	<	0.4	5.0	8.00%	STEL	19800630
348	028A	3	P	<	0.4	5.0	8.00%	STEL	19800630
349	028A	3	A	<	0.4	5.0	8.00%	STEL	19800630
350	ETFA	4	P		0.4	3.0	13.30%	STEL	19920901
351	01AA	4	P	<	0.4	3.0	13.30%	STEL	19920901
352	01AA	4	P	<	0.4	3.0	13.30%	STEL	19920901
353	005A	681	P	<	0.4	5.0	8.00%	STEL	19800630
354	005A	681	P	<	0.4	5.0	8.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

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	A	B	C	D	E	F	G	H	I
355	046B	751	P	<	0.4	5.0	8.00%	STEL	19800630
356	008D	831	A		0.4	5.0	8.00%	STEL	19800630
357	002A	852	P		0.4	3.0	13.30%	STEL	19920901
358	030D	3	P		0.39	3.0	13.00%	STEL	19920901
359	ETFA	4	P		0.39	5.0	7.80%	STEL	19800630
360	001B	735	P		0.39	5.0	7.80%	STEL	19800630
361	ETFA	4	A	<	0.38	5.0	7.60%	STEL	19800630
362	057A	7	P	<	0.37	3.0	12.30%	STEL	19920901
363	501B	222	P	<	0.37	3.0	12.30%	STEL	19920901
364	ETFA	4	P	<	0.36	5.0	7.20%	STEL	19800630
365	WTFA	4	P		0.35	3.0	11.70%	STEL	19920901
366	008A	15	P		0.35	5.0	7.00%	STEL	19800630
367	017K	651	P		0.35	6.0	5.80%	STEL	19981015
368	009A	735	P		0.35	3.0	11.70%	STEL	19920901
369	ETFA	4	P		0.32	6.0	5.30%	STEL	19981015
370	003C	16	P		0.31	3.0	10.30%	STEL	19920901
371	007C	394	P		0.31	6.0	5.20%	STEL	19981015
372	028A	3	A		0.3	3.0	10.00%	STEL	19920901
373	ETFA	4	P	<	0.3	5.0	6.00%	STEL	19800630
374	ETFA	4	P		0.3	5.0	6.00%	STEL	19800630
375	ETFA	4	P	<	0.3	3.0	10.00%	STEL	19920901
376	WTFA	4	P		0.3	3.0	10.00%	STEL	19920901
377	01AA	4	P	<	0.3	3.0	10.00%	STEL	19920901
378	RHTA	5	P	<	0.3	5.0	6.00%	STEL	19800630
379	B3MA	5	P	<	0.3	3.0	10.00%	STEL	19920901
380	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
381	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
382	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
383	03AB	9	P	<	0.3	5.0	6.00%	STEL	19800630
384	006D	15	P	<	0.3	5.0	6.00%	STEL	19800630
385	501B	222	P	<	0.3	3.0	10.00%	STEL	19920901
386	072B	711	P		0.3	5.0	6.00%	STEL	19800630
387	010A	821	P		0.3	6.0	5.00%	STEL	19981015
388	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
389	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
390	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
391	010T	821	P		0.29	3.0	9.70%	STEL	19920901
392	008D	831	P		0.29	6.0	4.80%	STEL	19981015
393	WTFA	4	P	<	0.28	3.0	9.30%	STEL	19920901
394	B3AA	5	P	<	0.28	3.0	9.30%	STEL	19920901
395	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
396	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
397	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
398	048A	632	P		0.28	3.0	9.30%	STEL	19920901
399	ETFA	4	P		0.27	5.0	5.40%	STEL	19800630
400	03AB	9	P	<	0.27	6.0	4.50%	STEL	19981015
401	03AB	9	P	<	0.27	6.0	4.50%	STEL	19981015
402	009C	15	P	<	0.27	3.0	9.00%	STEL	19920901
403	003C	16	P	<	0.27	6.0	4.50%	STEL	19981015
404	001D	16	P		0.27	3.0	9.00%	STEL	19920901
405	007C	394	P		0.27	6.0	4.50%	STEL	19981015

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
406	ETFA	4	P	<	0.26	5.0	5.20%	STEL	19800630
407	01AA	4	P	<	0.26	3.0	8.70%	STEL	19920901
408	DRFA	5	P		0.26	3.0	8.70%	STEL	19920901
409	057E	7	P	<	0.26	3.0	8.70%	STEL	19920901
410	005A	681	P		0.26	6.0	4.30%	STEL	19981015
411	001C	4	P		0.25	3.0	8.30%	STEL	19920901
412	001B	4	A		0.25	3.0	8.30%	STEL	19920901
413	B3AA	5	P	<	0.25	3.0	8.30%	STEL	19920901
414	HT2A	5	P		0.25	3.0	8.30%	STEL	19920901
415	014G	7	P	<	0.25	6.0	4.20%	STEL	19981015
416	007C	394	P	<	0.25	3.0	8.30%	STEL	19920901
417	007C	394	P	<	0.25	3.0	8.30%	STEL	19920901
418	072C	711	P	<	0.25	6.0	4.20%	STEL	19981015
419	072C	711	P	<	0.25	6.0	4.20%	STEL	19981015
420	072C	711	A	<	0.25	6.0	4.20%	STEL	19981015
421	005A	808	P		0.25	3.0	8.30%	STEL	19920901
422	01AA	4	P	<	0.24	3.0	8.00%	STEL	19920901
423	HTSA	5	P		0.24	6.0	4.00%	STEL	19981015
424	TRAK	5	P		0.24	6.0	4.00%	STEL	19981015
425	009C	15	P	<	0.24	3.0	8.00%	STEL	19920901
426	003C	16	P		0.24	3.0	8.00%	STEL	19920901
427	001D	16	P	<	0.24	3.0	8.00%	STEL	19920901
428	048A	632	P		0.24	3.0	8.00%	STEL	19920901
429	001E	735	P		0.24	5.0	4.80%	STEL	19800630
430	009A	735	A		0.24	6.0	4.00%	STEL	19981015
431	010A	821	P		0.24	6.0	4.00%	STEL	19981015
432	010A	821	P	<	0.24	6.0	4.00%	STEL	19981015
433	008D	831	A	<	0.24	3.0	8.00%	STEL	19920901
434	ETFA	4	P		0.23	5.0	4.60%	STEL	19800630
435	DPAA	5	A	<	0.23	5.0	4.60%	STEL	19800630
436	010S	821	P		0.23	3.0	7.70%	STEL	19920901
437	137A	3	P		0.22	3.0	7.30%	STEL	19920901
438	005B	398	A		0.22	3.0	7.30%	STEL	19920901
439	072C	711	A	<	0.22	6.0	3.70%	STEL	19981015
440	ETFA	4	P	<	0.21	3.0	7.00%	STEL	19920901
441	001C	681	P	<	0.21	3.0	7.00%	STEL	19920901
442	010T	821	P		0.21	5.0	4.20%	STEL	19800630
443	028A	3	P		0.2	5.0	4.00%	STEL	19800630
444	ETFA	4	P	<	0.2	5.0	4.00%	STEL	19800630
445	01AA	4	P	<	0.2	5.0	4.00%	STEL	19800630
446	WTFA	4	P		0.2	3.0	6.70%	STEL	19920901
447	WTFA	4	P	<	0.2	3.0	6.70%	STEL	19920901
448	WTFA	4	P	<	0.2	3.0	6.70%	STEL	19920901
449	001A	4	P	<	0.2	3.0	6.70%	STEL	19920901
450	01AA	4	P	<	0.2	3.0	6.70%	STEL	19920901
451	ETFA	4	A	<	0.2	3.0	6.70%	STEL	19920901
452	WTFA	4	A	<	0.2	3.0	6.70%	STEL	19920901
453	B3AA	5	P	<	0.2	3.0	6.70%	STEL	19920901
454	DPAA	5	A	<	0.2	5.0	4.00%	STEL	19800630
455	009C	15	P	<	0.2	3.0	6.70%	STEL	19920901
456	003D	395	P	<	0.2	5.0	4.00%	STEL	19800630

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Acrylic Acid Data Summary (1980 to Present)

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	A	B	C	D	E	F	G	H	I
457	017K	632	P		0.2	3.0	6.70%	STEL	19920901
458	004A	912	P		0.2	5.0	4.00%	STEL	19800630
459	HTGA	5	P	<	0.19	6.0	3.20%	STEL	19981015
460	HTSA	5	P	<	0.19	3.0	6.30%	STEL	19920901
461	010S	821	P	<	0.19	3.0	6.30%	STEL	19920901
462	01AA	4	P		0.18	5.0	3.60%	STEL	19800630
463	014N	7	P	<	0.18	6.0	3.00%	STEL	19981015
464	010A	821	P		0.18	6.0	3.00%	STEL	19981015
465	008D	831	P	<	0.18	6.0	3.00%	STEL	19981015
466	01AA	4	P	<	0.17	6.0	2.80%	STEL	19981015
467	01AA	4	P	<	0.17	6.0	2.80%	STEL	19981015
468	009A	4	P		0.17	3.0	5.70%	STEL	19920901
469	009C	15	P	<	0.17	3.0	5.70%	STEL	19920901
470	001D	16	P		0.17	3.0	5.70%	STEL	19920901
471	017K	632	A		0.17	5.0	3.40%	STEL	19800630
472	B3AA	5	P	<	0.16	3.0	5.30%	STEL	19920901
473	048A	632	P		0.16	3.0	5.30%	STEL	19920901
474	031A	2	P	<	0.15	15.0	1.00%	STEL	19780417
475	028A	3	A	<	0.15	5.0	3.00%	STEL	19800630
476	009A	4	P	<	0.15	6.0	2.50%	STEL	19981015
477	059B	7	A	<	0.15	5.0	3.00%	STEL	19800630
478	059B	7	A	<	0.15	5.0	3.00%	STEL	19800630
479	048A	632	P		0.15	5.0	3.00%	STEL	19800630
480	002C	632	P		0.15	5.0	3.00%	STEL	19800630
481	CRYA	3	A		0.14	5.0	2.80%	STEL	19800630
482	ETFA	4	P	<	0.14	3.0	4.70%	STEL	19920901
483	WTFA	4	P	<	0.14	3.0	4.70%	STEL	19920901
484	004F	397	P	<	0.14	3.0	4.70%	STEL	19920901
485	010A	821	P		0.14	6.0	2.30%	STEL	19981015
486	002A	852	P	<	0.14	6.0	2.30%	STEL	19981015
487	048A	632	P		0.138	5.0	2.80%	STEL	19800630
488	002C	632	P		0.138	5.0	2.80%	STEL	19800630
489	WTFA	4	P	<	0.13	3.0	4.30%	STEL	19920901
490	01AA	4	P	<	0.13	3.0	4.30%	STEL	19920901
491	008D	831	P		0.13	3.0	4.30%	STEL	19920901
492	008D	831	A	<	0.13	3.0	4.30%	STEL	19920901
493	01AA	4	P	<	0.12	6.0	2.00%	STEL	19981015
494	HTGA	5	P	<	0.12	3.0	4.00%	STEL	19920901
495	HTGA	5	P	<	0.12	3.0	4.00%	STEL	19920901
496	022A	622	P	<	0.12	3.0	4.00%	STEL	19920901
497	048A	632	P		0.12	3.0	4.00%	STEL	19920901
498	010A	821	P		0.12	6.0	2.00%	STEL	19981015
499	01AA	4	P	<	0.11	6.0	1.80%	STEL	19981015
500	ETFA	4	P	<	0.11	5.0	2.20%	STEL	19800630
501	HTGA	5	P	<	0.11	3.0	3.70%	STEL	19920901
502	HTXA	5	P		0.11	3.0	3.70%	STEL	19920901
503	08AF	9	P		0.11	3.0	3.70%	STEL	19920901
504	009C	15	P	<	0.11	3.0	3.70%	STEL	19920901
505	B3AR	5	P	<	0.101	3.0	3.40%	STEL	19920901
506	031A	2	P	<	0.1	5.0	2.00%	STEL	19800630
507	01AA	4	P	<	0.1	5.0	2.00%	STEL	19800630

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508	01AA	4	P	<	0.1	5.0	2.00%	STEL	19800630
509	WTFA	4	P	<	0.1	3.0	3.30%	STEL	19920901
510	ETFA	4	A	<	0.1	6.0	1.70%	STEL	19981015
511	HTEA	5	P		0.1	3.0	3.30%	STEL	19920901
512	HT2C	5	A	<	0.1	3.0	3.30%	STEL	19920901
513	005B	398	P		0.1	3.0	3.30%	STEL	19920901
514	005B	398	P	<	0.1	3.0	3.30%	STEL	19920901
515	017B	632	P	<	0.1	5.0	2.00%	STEL	19800630
516	017B	632	P	<	0.1	3.0	3.30%	STEL	19920901
517	017K	632	P	<	0.1	3.0	3.30%	STEL	19920901
518	072B	711	P	<	0.1	5.0	2.00%	STEL	19800630
519	001C	753	P	<	0.1	3.0	3.30%	STEL	19920901
520	010A	821	P	<	0.1	6.0	1.70%	STEL	19981015
521	008D	831	P	<	0.1	6.0	1.70%	STEL	19981015
522	008D	831	P	<	0.1	3.0	3.30%	STEL	19920901
523	008D	831	P	<	0.1	3.0	3.30%	STEL	19920901
524	008D	831	A	<	0.1	3.0	3.30%	STEL	19920901
525	072C	711	P	<	0.099	3.0	3.30%	STEL	19920901
526	WTFA	4	P	<	0.098	3.0	3.30%	STEL	19920901
527	WTFA	4	A	<	0.098	6.0	1.60%	STEL	19981015
528	01AA	4	P	<	0.092	6.0	1.50%	STEL	19981015
529	031A	2	P	<	0.09	15.0	0.60%	STEL	19780417
530	ETFA	4	P	<	0.09	3.0	3.00%	STEL	19920901
531	HT2A	5	P	<	0.09	3.0	3.00%	STEL	19920901
532	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
533	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
534	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
535	01AA	4	P	<	0.086	6.0	1.40%	STEL	19981015
536	001A	4	P	<	0.085	3.0	2.80%	STEL	19920901
537	005A	808	P	<	0.085	3.0	2.80%	STEL	19920901
538	005A	808	P	<	0.085	3.0	2.80%	STEL	19920901
539	OFFS	9	A	<	0.083	6.0	1.40%	STEL	19981015
540	01AA	4	P	<	0.082	3.0	2.70%	STEL	19920901
541	OFFS	9	A	<	0.081	6.0	1.40%	STEL	19981015
542	HR2A	5	P	<	0.08	3.0	2.70%	STEL	19920901
543	HR2A	5	P	<	0.08	3.0	2.70%	STEL	19920901
544	022A	622	P	<	0.08	3.0	2.70%	STEL	19920901
545	022E	622	P	<	0.08	3.0	2.70%	STEL	19920901
546	022A	622	P	<	0.08	3.0	2.70%	STEL	19920901
547	002C	632	P		0.08	3.0	2.70%	STEL	19920901
548	WTFA	4	P		0.079	5.0	1.60%	STEL	19800630
549	ETFA	4	P	<	0.078	3.0	2.60%	STEL	19920901
550	ETFA	4	P	<	0.077	3.0	2.60%	STEL	19920901
551	08AF	9	P		0.077	3.0	2.60%	STEL	19920901
552	100G	641	P		0.073	3.0	2.40%	STEL	19920901
553	01AA	4	P	<	0.072	3.0	2.40%	STEL	19920901
554	OFFS	9	A	<	0.072	6.0	1.20%	STEL	19981015
555	ETFA	4	P	<	0.071	3.0	2.40%	STEL	19920901
556	002B	808	A	<	0.071	3.0	2.40%	STEL	19920901
557	022A	622	P	<	0.07	3.0	2.30%	STEL	19920901
558	WTFA	4	A	<	0.068	3.0	2.30%	STEL	19920901

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"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
559	HT2A	5	P	<	0.068	3.0	2.30%	STEL	19920901
560	ETFA	4	P	<	0.067	3.0	2.20%	STEL	19920901
561	01AA	4	P	<	0.065	3.0	2.20%	STEL	19920901
562	01AA	4	P	<	0.065	3.0	2.20%	STEL	19920901
563	ETFA	4	A	<	0.065	3.0	2.20%	STEL	19920901
564	WTFA	4	P	<	0.064	3.0	2.10%	STEL	19920901
565	01AA	4	P	<	0.064	3.0	2.10%	STEL	19920901
566	ETFA	4	A	<	0.063	3.0	2.10%	STEL	19920901
567	WTFA	4	P	<	0.062	3.0	2.10%	STEL	19920901
568	01AA	4	P	<	0.062	3.0	2.10%	STEL	19920901
569	01AA	4	P	<	0.062	3.0	2.10%	STEL	19920901
570	HT2M	5	P	<	0.061	3.0	2.00%	STEL	19920901
571	005B	398	P	<	0.061	3.0	2.00%	STEL	19920901
572	008D	831	A	<	0.061	3.0	2.00%	STEL	19920901
573	01AA	4	P	<	0.06	5.0	1.20%	STEL	19800630
574	022A	622	P	<	0.06	3.0	2.00%	STEL	19920901
575	017K	632	P		0.06	3.0	2.00%	STEL	19920901
576	009C	681	P	<	0.058	6.0	1.00%	STEL	19981015
577	978A	840	A		0.058	3.0	1.90%	STEL	19920901
578	WTFA	4	A	<	0.056	3.0	1.90%	STEL	19920901
579	08AF	9	A	<	0.055	3.0	1.80%	STEL	19920901
580	WTFA	4	A	<	0.054	3.0	1.80%	STEL	19920901
581	03BC	9	P	<	0.051	3.0	1.70%	STEL	19920901
582	072D	711	P		0.051	3.0	1.70%	STEL	19920901
583	HTEA	5	P	<	0.05	3.0	1.70%	STEL	19920901
584	002C	632	P	<	0.05	3.0	1.70%	STEL	19920901
585	040D	821	P	<	0.05	3.0	1.70%	STEL	19920901
586	040D	821	P	<	0.05	3.0	1.70%	STEL	19920901
587	ETFA	4	A	<	0.048	3.0	1.60%	STEL	19920901
588	005A	681	A		0.048	3.0	1.60%	STEL	19920901
589	005A	681	P		0.045	3.0	1.50%	STEL	19920901
590	ETFA	4	P	<	0.044	3.0	1.50%	STEL	19920901
591	005A	681	P	<	0.044	6.0	0.70%	STEL	19981015
592	01AA	4	P	<	0.043	3.0	1.40%	STEL	19920901
593	002A	808	A	<	0.043	6.0	0.70%	STEL	19981015
594	735A	735	A	<	0.041	6.0	0.70%	STEL	19981015
595	005A	681	P	<	0.039	3.0	1.30%	STEL	19920901
596	735A	735	A	<	0.039	6.0	0.70%	STEL	19981015
597	735A	735	A	<	0.037	6.0	0.60%	STEL	19981015
598	735A	735	A	<	0.036	6.0	0.60%	STEL	19981015
599	009A	735	A	<	0.032	6.0	0.50%	STEL	19981015
600	DPAA	5	P	<	0.03	5.0	0.60%	STEL	19800630
601	002C	396	A	<	0.03	3.0	1.00%	STEL	19920901
602	DPAA	5	P	<	0.029	5.0	0.60%	STEL	19800630
603	008A	831	A	<	0.029	6.0	0.50%	STEL	19981015
604	DPAA	5	P	<	0.028	5.0	0.60%	STEL	19800630
605	DPAA	5	P	<	0.026	5.0	0.50%	STEL	19800630
606	03AB	9	P	<	0.024	3.0	0.80%	STEL	19920901
607	08AF	9	P	<	0.022	3.0	0.70%	STEL	19920901
608	WHSE	16	A	<	0.022	3.0	0.70%	STEL	19920901
609	TRAK	5	P	<	0.02	6.0	0.30%	STEL	19981015

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Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
610	B3AA	5	P	<	0.02	3.0	0.70%	STEL	19920901
611	008D	831	P	<	0.02	3.0	0.70%	STEL	19920901
612	978A	840	A	<	0.02	3.0	0.70%	STEL	19920901
613	DPAA	5	A	<	0.016	5.0	0.30%	STEL	19800630
614	013A	831	A	<	0.016	3.0	0.50%	STEL	19920901
615	03BC	9	P		0.015	3.0	0.50%	STEL	19920901
616	801D	3	A		0.013	5.0	0.30%	STEL	19800630
617	801D	3	A		0.013	5.0	0.30%	STEL	19800630
618	SPHB	9	A	<	0.013	6.0	0.20%	STEL	19981015
619	03AC	9	A	<	0.012	6.0	0.20%	STEL	19981015
620	072B	711	P	<	0.011	5.0	0.20%	STEL	19800630
621	ETFA	4	P	<	0.01	5.0	0.20%	STEL	19800630
622	RHTA	5	P	<	0.01	5.0	0.20%	STEL	19800630
623	08AF	9	A	<	0.0092	3.0	0.30%	STEL	19920901
624	001D	16	P	<	0.009	5.0	0.20%	STEL	19800630
625	003C	16	A		0.007	5.0	0.10%	STEL	19800630
626	017E	632	P		0.007	5.0	0.10%	STEL	19800630
627	RHTA	5	P	<	0.006	5.0	0.10%	STEL	19800630
628	501B	222	P	<	0.006	3.0	0.20%	STEL	19920901
629	501B	222	P	<	0.006	3.0	0.20%	STEL	19920901
630	001C	753	P		0.005	5.0	0.10%	STEL	19800630
631	DPAA	5	A	<	0.004	5.0	0.10%	STEL	19800630
632	017K	632	P	<	0.001	3.0	0.03%	STEL	19920901
633			Average =		1.8464				
634			Geometric Mean =		0.4759				
635			Median =		0.5				
636	214 values of 1 ppm or over for 34% of total						(Includes limit of detection samples)		
637	126 values of 2 ppm or over for 20% of total						(Includes limit of detection samples)		
638	46 values of 5 ppm or over for 7% of total						(Includes limit of detection samples)		
639	17 values of 10 ppm or over for 3% of total						(Includes limit of detection samples)		
640	Range = < 0.001 (or nondetect at the limit of detection of the analytical method								
641	used at the time) to 63 ppm								

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

FINAL REPORT

on

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

to

Rohm and Haas Co.
727 Norristown Rd.
Springhouse, PA 19477

September, 1995

by

Michael J. Brooker and Michael E. Placke

BATTELLE
505 King Avenue
Columbus, Ohio 43201-2693

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

Study Title: Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA)

Battelle Study Number: SC940138

This study was conducted in compliance with EPA GLP Regulations 40 CFR Part 792. This study was conducted according to the study protocol and Battelle's Standard Operating Procedures and to the best of my knowledge the data presented accurately reflect the results of this study.

Michael J. Brooker 9/12/95

Michael J. Brooker, B.S.
Study Director

FINAL REPORT

on

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

September, 1995

Michael J. Brooker, B.S.
Study Director

September 12, 1995
Date

Michael E. Placke, Ph.D., DABT
Program Manager

9/12/95
Date

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to the study director and management as follows:

Phase Inspected	Date Inspected	Date Reported to Study Director	Date of Report to Management
Randomization	12//08/94	1/04/95	1/04/95
Acclimation	12/16/94	1/04/95	1/04/95
Body weights	12/16/94	1/04/95	1/04/95
Euthanasia	12/16/94	1/04/95	1/04/95
Infrared spectroscopy analysis	12/16/94	1/04/95	1/04/95
Necropsy/tissue collection	12/16/94	1/04/95	1/04/95
Respiratory parameters collection	12/16/94	1/04/95	1/04/95
Test substance administration - inhalation	12/16/94	1/04/95	1/04/95
Audit: Study File	2/06/95	2/06/95	3/27/95
Audit: Draft Final Report	2/06/95	2/06/95	9/12/95
Audit: Final Report	9/12/95	9/12/95	9/12/95

Kathleen E. Reed 9-12-95

Quality Assurance Unit Date

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SUMMARY

The objective of this study was to evaluate the acute toxicity of Ethyl Acrylate (EA) and Acrylic Acid (AA) in monkeys after a single inhalation exposure to one of the two test substances. Five groups of primates, three animals each, were exposed via head-only inhalation exposure to a common target vapor concentration (75 ppm) of one of the two test substances or filtered air (controls). Each animal received a single exposure of either three or six hour duration. Animals used on study were from a pool of animals maintained in the Battelle Animal Facility and were in good health prior to treatment.

The achieved mean test substance vapor concentration values were all within eight percent of the target concentration and the percent relative standard deviations were all less than 10 percent. The individual animal inhaled doses for Ethyl Acrylate ranged from 13.9 mg/kg (animal #202) to 36.9 mg/kg (animal #302). The inhaled doses for Acrylic Acid ranged from 12.7 mg/kg (animal #401) to 35.2 mg/kg (animal #503). All animals survived the exposures in good condition. No clinical signs of toxicity were observed and no treatment related findings were observed during the gross pathological examination. All protocol required tissues were shipped to Dr. Jack Harkema at Michigan State University for further evaluation.

The histopathologic data and evaluation will be added to the report at a later date by the Sponsor.

1.0 INTRODUCTION

The objective of this study was to evaluate the acute toxicity of Ethyl Acrylate (EA) and Acrylic Acid (AA) in monkeys after a single inhalation exposure. Rohm and Haas Inc. was the Project Sponsor. Dr. Clay Frederick was the designated Sponsor Project Monitor and approved the study protocol. The study was conducted in compliance with the EPA guidelines (40 CFR Part 792) and was listed on Battelle's list of regulated studies. The study protocol, amendments to the protocol, and any deviations from the protocol are contained in Appendix A. The study was conducted at Battelle Columbus Operations under the direction of Mr. Michael J. Brooker. The study was initiated on November 22, 1994 with the signing of the protocol and completed on September 12, 1995 with the signing of the final report.

2.0 MATERIALS AND METHODS

2.1 Experimental Design

Five groups of primates, three animals per group, were exposed via head-only inhalation exposure to one target concentration (75 ppm) of one of vapors of the two test compounds or filtered air (controls). Each animal received a single exposure for either three or six hour duration. The following table details the treatment groups:

Group Number	Test Substance	No. of Animals	Vapor Concentration (ppm)	Exposure Duration (hours)
1	Air Control	3	0	6
2	Ethyl Acrylate	3	75	3
3	Ethyl Acrylate	3	75	6
4	Acrylic Acid	3	75	3
5	Acrylic Acid	3	75	6

A sixteenth animal (non-exposed) was anesthetized, euthanized and necropsied for magnetic resonance image analysis by Dr. Kevin Morgan at the Chemical Institute of Industrial Toxicology (CIIT).

2.2 Test Substances

Two different test substances, Ethyl Acrylate and Acrylic Acid, were received from Rohm and Haas. Approximately 250 mL of each compound was received on November 22, 1994. The lot number for the Ethyl Acrylate was TD93-047. The lot number for the Acrylic Acid was TD94-095. The test substances were stored at room temperature. No expiration dates were listed for either of the test substances.

2.3 Test Substance Identity, Purity and Stability

The test substance identity, purity and stability were the responsibility of the Project Sponsor.

2.4 Inhalation Methods

2.4.1 Test Substance Generation and Delivery

Both of the test substances were generated in a similar manner. A small amount of the liquid test substance was placed in a 25 mL midget impinger and a measured flow of nitrogen was bubbled through the test substance in the impinger, vaporizing the test substance. The resultant vapors were ducted directly to the exposure plenum.

2.4.2 Exposure System

The output of the vapor generator (impinger) was delivered directly into a stainless steel vessel used as a dilution plenum. Within the plenum, Hepa filtered compressed air was added as dilution and carrier air to achieve a total flow through the system of 40 Liters per minute. The test atmosphere was transported through stainless steel tubing to each of the exposure helmets. Stainless steel venturi's (0.169 inch throat) were placed into the delivery line just prior to the exposure helmets.

The exposure helmets were constructed of 8-inch diameter acrylic cylinder approximately 6 inches tall. An air inlet was placed tangential to the radius near the top of the helmet. This produced a swirling effect within the helmet as air was drawn from smaller ports near the bottom of the helmet. The bias flow through each of the helmets was regulated at 10 L/min. An additional 10 liters per minute was supplied to the monitoring system.

2.4.3 Pulmonary Function Measurements

The volume of test atmosphere inhaled during exposure was determined for each animal by measuring the flow changes into the helmet through the venturi. Pressure drop at the throat of the venturi was monitored with a Validyne pressure transducer. Signals from the transducer were amplified by PO-NE-MAH preamplifiers for variable reluctance transducers.

A flow versus voltage relationship was documented for each venturi/amp/transducer set-up using a calibrated mass flow meter. Based upon the fluctuations in airflow through the venturi, the

respiration rate, and tidal volume were measured for each animal. Additionally, the total inhaled volume was calculated for each animal during the exposure period.

2.4.4 Test Substance Atmosphere Concentration Analysis

An infrared spectrophotometer system was used to monitor the concentration of the test substances in the exposure atmospheres. The Miran-980 infrared spectrometer (IR) Wilks (Foxboro Company, South Norfolk, CT) is a single-beam spectrometer, equipped with an adjustable cell pathlength (0.75 to 20.25 meters), and can be operated over a wavelength range from 2.5 to 14.5 micrometers (μm). Prior to initiating exposures a thorough calibration of the MIRAN-980 was completed. The wavelengths were selected based on absorbance versus wavelength scans of test substance standards. A reference wavelength was used to correct for instrument drift.

After selecting the sample location and waiting the required flushing time (approximately 5 minutes was needed at 10 L/minute air flow), the operator closed the outlet valve from the IR instrument, recorded the time and cell pressure, and initiated the recording of absorbance readings. Three successive absorbance readings were taken for the analytical wavelength of interest. The average of the three successive readings was used as a single analysis in subsequent calculations, substantially reducing analytical variability.

Samples were collected from the exposure plenum and the primate helmets during the pretest validation phase to determine the test substance concentration uniformity. After determining the concentration in the helmets was equal to the concentration in the exposure plenum, only the plenum was sampled during the animal exposures. Samples were collected at least twice per hour during the animal exposures.

2.4.5 Instrument Calibration

Calibration of the infrared spectrophotometer was based upon the injection of measured amounts of the respective test substances into the calibration loop of the IR cell. For the ethyl acrylate calibration, liquid ethyl acrylate was injected into the cell to give nominal concentrations of 19.5, 39, 78, and 117 ppm (0.5, 1, 2, and 3 μL injected, respectively). For the acrylic acid

calibration, liquid acrylic acid was injected into the cell to give nominal concentrations of 15.8, 31.6, 63.2, and 126.4 ppm (0.25, 0.5, 1, and 2 μL injected, respectively).

For each calibration, a control chart was developed with control limits determined from the multipoint calibration for a single point on the curve. The limit of acceptability was defined by the Study Director as 10 percent of the mean value of all injections for that point. During the study, the IR was challenged daily with a zero and a single calibration concentration. The results of the daily calibration check were compared immediately with the control chart limits before proceeding with the animal exposures.

2.4.6 Pre-Exposure System Validation

Prior to the start of exposures the system concentration uniformity was evaluated for each test compound. Additionally, a trial run was completed for each test compound to verify the readiness of the generation and exposure system.

2.5 Experimental Animals

A total of 15 Cynomolgus monkeys were required for the study. These animals were originally obtained from Charles River Primates, Inc. The animals were wild captured, young mature males and females that were previously quarantined and used in nonlethal experimentation at Battelle. During the original quarantine period, the animals tested negative to three sequential intradermal tuberculin tests at approximately two week intervals. At least one clinical pathology screen and fecal examination for internal parasites was made during the original quarantine period.

Cynomolgus monkeys were chosen as the test system since an extensive biochemical and physiological data base for the Cynomolgus monkey is available. In addition, there have been numerous studies concerned with the inhalation of agents by non-human primates.

2.5.1 Animal Housing and Environmental Conditions

All animals were individually housed in stainless steel, wire bottom cages. All housing and care practices conformed to the requirements stated in the NIH "Guide for Care and Use of

Laboratory Animals" (National Institute of Health Publication No. 86-23). All environmental conditions conformed to the Standard Operating Procedures of the Battelle Animal Facility.

All animals were fed Purina Certified Monkey chow twice daily during the pretest period and the study. Monkey diets were supplemented with fresh fruit and/or other supplements. Animals were not fed prior to exposure on the day of treatment. Water was provided *ad libitum* to all animals at all times other than restraint and exposure. There were no known contaminants in the food or water supplied to the animals which would adversely effect the results of this study.

2.6 Animal Randomization and Identification

Animals used on study were obtained from the pool of animals maintained in the Battelle Animal Facility. All animals were allocated to treatment groups prior to the start of any exposures. Animals were assigned randomly to treatment groups and identified by animal tattoo as well as cage cards with individual study numbers. A cross reference list of tattoo numbers and study numbers was maintained in the study file.

2.7 Clinical Pathology and Health Evaluations

A clinical pathology screening was completed prior to the allocation of animals into treatment groups along with a general health evaluation by the veterinary staff and study director. The following clinical pathology evaluations were conducted on each of the samples collected:

Hematology
Erythrocyte count (RBC)
Hematocrit (HCT)
Hemoglobin (HGB)
Leukocyte cell count (WBC)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count (PLT)
WBC differential

Serum Chemistry
Alanine aminotransferase (SGPT) (ALT)
Albumin (ALB)
Alkaline phosphatase (ALP)
Aspartate aminotransferase (SGOT) (AST)
Blood urea nitrogen (BUN)
Chloride (Cl)
Creatinine (CRE)
Glucose (GLU)
Potassium (K)
Sodium (Na)
Total protein (TP)

2.8 Body Weights

Body weights were determined during the pretest period for all animals and again on the day of treatment prior to the exposure.

2.9 Clinical Observations

Clinical observations were recorded twice (once prior and once post-exposure) for each animal on the day of treatment.

2.10 Necropsy

After the end of the exposure, each monkey was anesthetized with Ketamine and Sodium Pentobarbital and then euthanized by exsanguination. Immediately after death the head was removed from the carcass and both nasal passages were flushed via the nasopharyngeal orifice with 100-200 mL of 10 percent neutral buffered formalin. The eyes, skin, brain, lower jaw and musculature were then removed and discarded. The remainder of the head was preserved in fixative.

In addition, the lungs were removed and fixed by trachea cannulation with 10 percent neutral buffered formalin at 30 cm fixative pressure for at least two hours. The trachea and lungs were then stored in fixative as well. No other tissues were saved.

All tissues were shipped to Dr. Jack Harkema at Michigan State University for sectioning and histopathologic evaluation.

2.11 Statistical Evaluation of the Data

Group means and standard deviations will be reported for data sets. No group to group comparisons or statistical analyses will be completed.

3.0 RESULTS

3.1 Pre-Exposure Health Evaluation Results

The results of the pre-exposure health evaluations revealed that all the animals were healthy and acceptable for study. The results of the pre-exposure clinical pathology screenings are detailed in Tables 1 through 3. Table 1 contains the individual animal cell count data. Table 2 contains the individual animal WBC differential count data, and Table 3 contains the individual animal serum chemistry values. These data were reviewed in addition to a general physical evaluation of the animals and all were determined to be acceptable for study.

3.2 Body Weight Determinations

Body weight data was collected on each animal once pretest and again prior to exposure. These data are detailed in Table 4. Two animals ((#103 and #503) were slightly heavier than the protocol listed range of 2 to 5 kilograms. All other animals were within the protocol specified range.

3.3 Clinical Observations

All animals in group one (six hour air control) were normal before and after exposure. In group two (three hour Ethyl Acrylate) all animals were normal at the start of exposure however one animal, #201, developed a mild nasal discharge shortly after the start of exposure and was observed with labored breathing. The exposure was halted while the neck dam on this animal was adjusted and the exposure was restarted. At the end of exposure, the animal still had a nasal discharge however all other clinical signs were normal. The remaining two animals in group two were normal; however, animal #202 was noted as having an increased rate of eye blinking. There were no abnormal clinical observations recorded for any of the animals in groups three through five before or after exposure.

3.4 Necropsy Results

Three of the fifteen animals observed at necropsy were noted with abnormal findings. Animal #301 was noted with some pleural adhesions to diaphragm near the right lung. Animal #303 was noted with multiple adhesions between the lung lobes and the visceral and parietal pleura. The lesions in both animals were thought to be parasitic in origin and not treatment related. Animal #501 was noted to have multiple yellow nodules with black specks, possibly mites. This finding was also not thought to be treatment related.

3.5 Pre-Exposure System Validation

3.5.1 Infrared Analyzer Calibration Results

The infrared analyzer was calibrated for each test compound during the pre-exposure validation phase. The results of the calibration using Ethyl Acrylate are listed in Table 5. The calibration curve ranged from 19.5 ppm to 117 ppm. The percent relative standard deviations of the data from the repeat injections at each calibration point were less than two percent at all levels indicating good reproducibility in the amount of material provided as the standard and the response of the instrument to the injection.

The data in Table 6 are the results of the instrument calibration with Acrylic Acid. The calibration curve for Acrylic Acid ranged from 15.8 to 126.4 ppm. The percent relative standard deviations of the data from the repeat injections were less than 5 percent again showing good reproducibility and instrument response.

A nonlinear relationship was observed with each test substance over the range covered by the calibration. This nonlinear relationship would have introduced a significant bias in estimating concentration from absorbance values using a linear calibration curve. In order to compensate for this non-linearity, the calibration data was fit to a quadratic function. The regression procedure PROC REG in the Statistical Analysis System (SAS®) software package was used to calculate the regression parameters.

3.5.2 System Uniformity and Trial Run Results

The exposure system was evaluated for the uniformity of the test atmosphere in the plenum and the three exposure helmets with each compound. Table 7 (EA) and Table 8 (AA) contain the data from these analyses. Each compound showed a uniform distribution throughout the exposure system. A comparison of the mean value from the samples collected in the plenum and the mean value for the samples collected within the different exposure helmets revealed that the different locations were within 10 percent of each other for both test compounds.

The pretest trial run data are contained in Table 9 (EA) and Table 10 (AA). The results indicated the generation system was operating at the target concentration and was stable over time. The mean test substance concentration value was 76.13 ppm (101.5 percent of target) for the Ethyl Acrylate and 80.98 ppm (108 percent of target) for the Acrylic Acid.

3.5.3 Test Substance Concentrations

The mean test substance concentration data for each of the exposure groups are listed in Table 11. Table 12 contains the individual concentration analyses by exposure group. The mean test substance concentration values were all within eight percent of the target concentration and the percent relative standard deviations were all less than 10 percent. The mean concentration values were also calculated in a mass to volume measurement (mg/L), as well. These values were calculated using the following formula:

$$C_{ppm} = C_{mg/L} * 22.414 \text{ X } 10^3/mw * T/273 * 760/P$$

where

C is the concentration
mw is the molecular weight of the compound
T is the temperature in degrees Kelvin (298)
P is standard pressure (760 mmHg)

3.5.4 Pulmonary Function Measurements

The individual animal mean respiration rate (b/min), tidal volume, and total inhaled volume are listed in Table 13. The mean respiration rates ranged from 33.2 (animal #202) to 61.0 (animal #103) breathes per minute. The mean tidal volume measurements ranged from 0.019 L (animal #301) to 0.049 L (animal #503). The total inhaled volumes for the three hour exposures ranged from 147.24 liters (animal #202) to 314.39 liters (animal #403). The total inhaled volumes for the six hour exposures ranged from 294.55 liters (animal #301) to 776.14 liters (animal #503).

3.5.5 Inhaled Dose Estimates

The inhaled dose was calculated for each animal based on it's body weight, mean test substance concentration value and total inhaled volume. The group mean inhaled dose values are listed in Table 14. The individual animal values are listed in Table 15. The individual animal inhaled doses for Ethyl Acrylate ranged from 13.9 mg/kg (animal #202) to 36.9 mg/kg (animal #302). The inhaled doses for Acrylic Acid ranged from 12.7 mg/kg (animal #401) to 35.2 mg/kg (animal #503).

4.0 DISCUSSION

The objective of this study was to evaluate the acute toxicity of Ethyl Acrylate (EA) and Acrylic Acid (AA) in monkeys after a single inhalation exposure. Five groups of three animals each were exposed via head-only inhalation exposure to one target concentration (75 ppm) of one of the two test compounds or filtered air (controls). Each animal received a single exposure of either three or six hour duration. Animals used on study were obtained from the pool of animals maintained in the Battelle Animal Facility and were found to be in good health prior to treatment.

The mean test substance concentration values were all within eight percent of the target concentration and the percent relative standard deviations were all less than 10 percent. The individual animal inhaled doses for Ethyl Acrylate ranged from 13.9 mg/kg (animal #202) to 36.9 mg/kg (animal #302). The inhaled doses for Acrylic Acid ranged from 12.7 mg/kg (animal #401) to 35.2 mg/kg (animal #503). All animals survived the exposures in good condition. No clinical signs of toxicity were noted and no treatment related findings were recorded during the gross pathological examination. All protocol required tissues were shipped to Dr. Jack Harkema for further evaluation.

The histopathologic data and evaluation will be added to the report at a later date by the Sponsor.

5.0 SPECIMEN STORAGE AND RECORD ARCHIVES

All remaining test substances will be returned to the Sponsor after acceptance of the final report. All original records required to reconstruct the conduct of the study will be shipped to the Sponsor after acceptance of the final report. A copy of the entire study file and final report will be archived at Battelle. Battelle will not retain any specimens or tissues.

6.0 ACKNOWLEDGMENTS

Members of the Battelle General Toxicology, Animal Resources, and Pathology Departments whose signatures appear in the report or in the study records are acknowledged for their participation in the conduct of the study. The names of the principal contributors in this study are listed below:

Principal Contributors

Name	Study Role	Department
Michael J. Brooker, B.S.	Study Director	General Toxicology
Russ Antel, A.S., VT, L.A.T.G.	Primary Technician	Animal Resources
Allen Singer, D.V.M., D.A.C.V.P., D.A.B.T	Study Pathologist	Pathology
Michael J. Ryan, D.V.M., Ph.D., D.A.B.T., D.A.C.V.P.	Clinical Pathologist	Pathology
Michael E. Placke, Ph.D., D.A.B.T.	Senior Program Manager	Preclinical Drug Development

Table 1. Pre-Exposure Individual Animal Cell Count Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	WBC (10^3/mm^3)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet (10^3/mm^3)	RBC (10^6/mm^3)
122-55M	5.6	11.6	36.8	61.3	19.3	31.5	350	6.01
53-283M	7.1	12.3	40.7	58.6	17.7	30.2	445	6.95
73-2M	15.7	10.7	34.3	63.8	19.9	31.2	298	5.38
73-32M	5.8	11.8	40.6	59.3	17.3	29.1	413	6.84
73-6M	6.3	12.0	38.4	57.7	18.0	31.3	569	6.65
73-410M	10.2	12.4	42.0	63.7	18.8	29.5	315	6.59
73-461M	2.3	12.7	41.0	60.7	18.8	31.0	296	6.75
30-537F	17.3	8.8	27.4	56.4	18.1	32.1	323	4.85
30-544F	9.1	10.7	34.1	59.8	18.7	31.4	268	5.71
53-198F	5.2	9.5	31.6	52.4	15.7	30.1	254	6.04
53-203F	9.6	11.0	36.4	57.2	17.3	30.2	623	6.36
53-295F	3.4	10.0	33.8	56.9	16.8	29.6	357	5.94
63-290F	3.8	9.5	30.5	65.4	20.4	31.1	356	4.66
63-362F	3.4	10.6	35.0	57.6	17.4	30.3	253	6.08
63-372F	8.6	11.5	36.4	60.3	19.1	31.6	431	6.03

Table 2. Pre-Exposure Individual Animal WBC Differential Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Segmented Neutrophils (%)	Band Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Nucleated RBC's (nRBC/100WBC)	Reticulocytes (%)
122-55M	51	0	30	15	4	0	0	0.4
53-283M	25	0	66	7	2	0	0	0.1
73-2M	80	0	8	12	0	0	0	0.1
73-32M	30	0	62	5	2	1	0	0.1
73-6M	37	0	51	6	5	0	0	0.1
73-410M	53	0	38	9	0	0	0	0.3
73-461M	38	0	47	4	10	1	0	0.2
30-537F	57	0	38	5	0	0	0	1.3
30-544F	28	0	65	3	4	0	0	0.5
53-198F	22	0	71	4	3	0	0	0.2
53-203F	65	0	22	8	5	0	0	0.3
53-295F	15	0	68	14	2	0	0	0.2
63-290F	36	0	51	4	6	0	0	0.6
63-362F	58	0	36	1	3	2	0	0.1
63-372F	52	0	45	1	2	0	0	0.3

Table 3. Pre-Exposure Individual Animal Serum Chemistry Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	ALP (IU/L)	AST (IU/L)	ALT (IU/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	BUN (mg/dL)	Creatine (mg/dL)	Na (mEq/L)	K (mEq/L)	Chloride (mEq/L)
122-55M	603	33	29	6.6	3.9	61	19	1.1	148	3.8	107
53-283M	1250	22	45	7.5	4.8	62	17	0.8	148	3.5	111
73-2M	759	23	41	7.1	4.0	80	15	1.2	144	3.5	101
73-32M	1420	34	22	7.3	4.5	47	20	0.9	150	4.0	107
73-6M	1126	21	27	6.9	4.5	57	21	0.8	149	3.5	109
73-410M	2025	30	52	7.1	4.1	55	22	0.8	152	3.3	114
73-461M	1425	22	44	7.1	4.2	56	20	1.0	146	3.4	108
30-537F	1531	17	40	6.6	2.7	53	10	0.8	147	3.2	108
30-544F	317	24	43	7.7	4.1	72	17	0.8	147	2.9	109
53-198F	1093	18	15	6.5	4.0	68	16	0.7	148	3.6	111
53-203F	1120	22	25	6.3	4.1	58	20	0.8	148	3.9	110
53-295F	571	26	19	6.6	3.9	56	20	0.8	147	3.4	114
63-290F	705	32	65	7.2	4.2	54	19	0.7	148	3.5	109
63-362F	919	38	50	7.6	4.3	58	15	0.8	147	3.7	112
63-372F	630	22	31	7.4	4.6	62	20	0.9	148	3.6	109

Table 4. Individual Animal Body Weight Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Animal Study Number	Exposure Date	Body Weight (kg)
73-461M	101	12/14/94	4.06
73-32M	102	12/14/94	3.97
122-55M	103	12/14/94	5.26
53-203F	201	12/16/94	2.87
63-362F	202	12/16/94	3.17
53-295F	203	12/16/94	3.13
63-372F	301	12/19/94	2.94
63-290F	302	12/19/94	2.75
30-537F	303	12/19/94	2.58
53-283M	401	12/20/94	4.04
53-198F	402	12/20/94	2.73
73-6M	403	12/20/94	4.81
30-544F	501	12/21/94	2.65
73-410M	502	12/21/94	3.98
73-2M	503	12/21/94	5.07

Table 5. Ethyl Acrylate Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Amount Injected (μL)	Calculated Concentration (ppm)	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.	Grand Mean	Standard Deviation	Percent Rel. Std. Deviation
0.5	19.5	0.3202	0.3204	0.3206	0.3204			
0.5	19.5	0.3189	0.3203	0.3201	0.3198	0.3176	0.0044	1.38
0.5	19.5	0.3122	0.3127	0.3125	0.3125			
1	39	0.5028	0.5036	0.5024	0.5029			
1	39	0.5079	0.5076	0.5085	0.5080	0.5056	0.0026	0.51
1	39	0.5054	0.5062	0.5063	0.5060			
2	78	0.6808	0.6805	0.6815	0.6809			
2	78	0.6835	0.6852	0.6853	0.6847	0.6827	0.0019	0.28
2	78	0.6817	0.6833	0.6825	0.6825			
3	117	0.7979	0.7984	0.8002	0.7988			
3	117	0.7953	0.7955	0.7960	0.7956	0.7999	0.0035	0.43
3	117	0.8031	0.8012	0.8007	0.8017			
3	117	0.8053	0.8021	0.8031	0.8035			

Table 6. Acrylic Acid Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Amount Injected (μL)	Calculated Concentration (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.	Grand Mean	Standard Deviation	Percent Rel. Std. Deviation
0.25	15.8	0.0008	0.0979	0.0977	0.0974	0.0977			
0.25	15.8	0.0012	0.1050	0.1049	0.1046	0.1048	0.0994	0.0047	4.77
0.25	15.8	0.0028	0.0956	0.0961	0.0956	0.0958			
0.5	31.6	0.0051	0.1984	0.1978	0.1969	0.1977			
0.5	31.6	0.0055	0.2102	0.2091	0.2094	0.2096	0.2038	0.0060	2.92
0.5	31.6	0.0053	0.2041	0.2039	0.2040	0.2040			
1	63.2	0.0120	0.3517	0.3511	0.3506	0.3511			
1	63.2	0.0124	0.3511	0.3515	0.3513	0.3513	0.3530	0.0031	0.88
1	63.2	0.0124	0.3574	0.3567	0.3556	0.3566			
2	126.4	0.0408	0.5740	0.5750	0.5737	0.5742			
2	126.4	0.0401	0.5740	0.5728	0.5739	0.5736	0.5724	0.0026	0.45
2	126.4	0.0389	0.5702	0.5685	0.5699	0.5695			

Table 7. Ethyl Acrylate Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/9/94)	Sample Location	Concentration (ppm)
14	Plenum	77.76
15	Helmet - 1	72.60
16	Plenum	78.17
17	Helmet - 2	76.59
18	Plenum	78.52
19	Helmet - 3	77.84
20	Plenum	75.83
	Plenum Mean (Std. Dev.)	77.57 (1.2)
	Helmet Mean (Std. Dev.)	75.68 (2.7)

Table 8. Acrylic Acid Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/12/94)	Sample Location	Concentration (ppm)
14	Plenum	81.21
15	Helmet - 1	71.03
16	Plenum	80.34
17	Helmet - 2	75.35
18	Plenum	80.15
19	Helmet - 3	79.80
20	Plenum	81.98
	Plenum Mean (Std. Dev.)	80.92 (0.8)
	Helmet Mean (Std. Dev.)	75.39 (4.4)

Table 9. Ethyl Acrylate Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/9/94)	Sample Location	Concentration (ppm)
14	Plenum	77.76
16	Plenum	78.17
18	Plenum	78.52
20	Plenum	75.83
21	Plenum	75.51
22	Plenum	74.64
23	Plenum	74.38
24	Plenum	74.23
	Mean (% Rel. Std. Dev.)	76.13 (2.3)
	Percent of Target	101.5

Table 10. Acrylic Acid Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/12/94)	Sample Location	Concentration (ppm)
14	Plenum	81.21
16	Plenum	80.34
18	Plenum	80.15
20	Plenum	81.98
21	Plenum	81.89
22	Plenum	79.93
23	Plenum	81.35
	Mean (% Rel. Std. Dev.)	80.98 (1.0)
	Percent of Target	108.0

Table 11. Mean Test Substance Concentration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Group Number	Compound	Duration (hrs)	Mean Concentration (ppm)	Standard Deviation	% Relative Standard Deviation	Percent of Target	Calculated Concentration (mg/L)
1	Air Control	6	--	--	--	--	0
2	EA	3	73.37	6.56	8.94	97.8	0.30
3	EA	6	76.28	1.85	2.42	101.7	0.31
4	AA	3	80.51	3.61	4.48	107.3	0.24
5	AA	6	78.06	3.12	4.00	104.1	0.23

Table 12. Test Substance Concentration Data (Individual Analyses) for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample Collected	Ethyl Acrylate Three Hour Exposure Concentration (ppm)	Ethyl Acrylate Six Hour Exposure Concentration (ppm)	Acrylic Acid Three Hour Exposure Concentration (ppm)	Acrylic Acid Six Hour Exposure Concentration (ppm)
1	76.88	79.49	74.90	73.93
2	76.51	79.88	81.68	76.64
3	75.95	77.23	83.40	78.48
4	75.23	76.32	84.93	77.67
5	75.60	75.64	78.84	78.71
6	60.03	74.60	79.28	83.02
7		76.15		80.81
8		76.62		82.72
9		75.30		78.51
10		75.11		78.03
11		75.30		75.04
12		73.70		73.19
Mean	73.37	76.278	80.51	78.06

Table 12. Test Substance Concentration Data (Individual Analyses) for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample Collected	Ethyl Acrylate Three Hour Exposure Concentration (ppm)	Ethyl Acrylate Six Hour Exposure Concentration (ppm)	Acrylic Acid Three Hour Exposure Concentration (ppm)	Acrylic Acid Six Hour Exposure Concentration (ppm)
1	76.88	79.49	74.90	73.93
2	76.51	79.88	81.68	76.64
3	75.95	77.23	83.40	78.48
4	75.23	76.32	84.93	77.67
5	75.60	75.64	78.84	78.71
6	60.03	74.60	79.28	83.02
7		76.15		80.81
8		76.62		82.72
9		75.30		78.51
10		75.11		78.03
11		75.30		75.04
12		73.70		73.19
Mean	73.37	76.278	80.51	78.06

Table 13. Individual Animal Pulmonary Function Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal Number	Mean Respiration Rate (b/min)	Mean Tidal Volume (L)	Total Inhaled Volume (L)
101	55.4	.032	623.18
102	38.0	.028	387.58
103	61.0	.038	770.92
201	42.4	.021	154.13
202	33.2	.024	147.24
203	53.0	.026	251.72
301	44.2	.019	294.55
302	40.1	.023	327.14
303	34.5	.025	295.68
401	44.4	.028	214.23
402	55.6	.023	214.37
403	43.4	.042	314.39
501	33.6	.029	309.83
502	39.4	.028	371.87
503	45.9	.049	776.14

Table 14. Group Mean Inhaled Dose Estimates for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Group Number	Compound	Duration (hrs)	Mean Inhaled Dose (mg/kg)	Standard Deviation	% Relative Standard Deviation
1	Air Control	6	--	--	--
2	EA	3	18.0	5.37	29.8
3	EA	6	34.5	3.03	8.77
4	AA	3	15.7	3.05	19.4
5	AA	6	27.9	6.90	24.7

Table 15. Individual Animal Estimated Inhaled Dose Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Body Weight (kg)	Test Compound	Concentration (mg/L)	Total Inhaled Volume (L)	Total Inhaled Dose (mg/kg)
101	4.06	Air	0.00	623.18	0.0
102	3.97	Air	0.00	387.58	0.0
103	5.26	Air	0.00	770.92	0.0
201	2.87	EA	0.30	154.13	16.1
202	3.17	EA	0.30	147.24	13.9
203	3.13	EA	0.30	251.72	24.1
301	2.94	EA	0.31	294.55	31.1
302	2.75	EA	0.31	327.14	36.9
303	2.58	EA	0.31	295.68	35.5
401	4.04	AA	0.24	214.23	12.7
402	2.73	AA	0.24	214.37	18.8
403	4.81	AA	0.24	314.39	15.7
501	2.65	AA	0.23	309.83	26.9
502	3.98	AA	0.23	371.87	21.5
503	5.07	AA	0.23	776.14	35.2

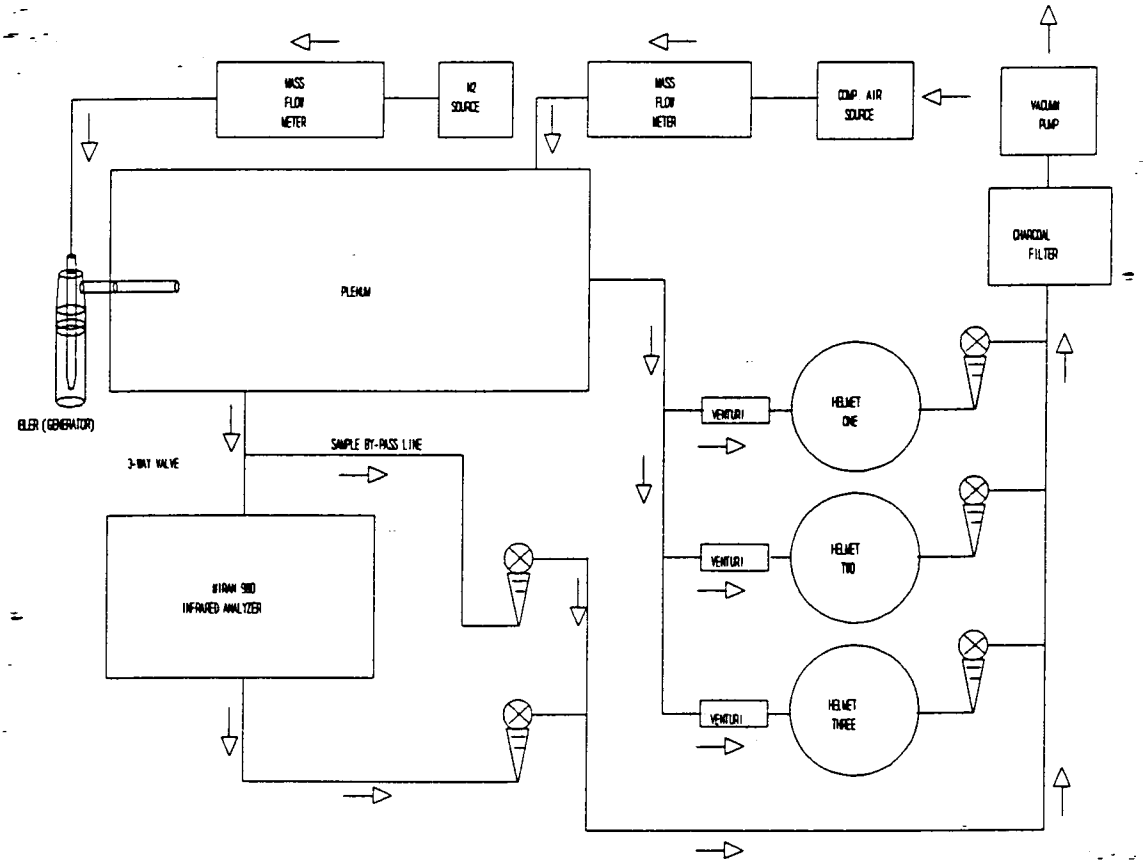

Figure 1. Schematic Diagram of Exposure System

APPENDIX A

STUDY PROTOCOL, AMENDMENTS, AND DEVIATIONS

Sponsor Study No.: 94P-227
Battelle Study No.: SC940138
November 22, 1994

STUDY PROTOCOL

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

Sponsor's Test Article: Ethyl Acrylate (EA) and Acrylic Acid (AA)

Prepared For: Rohm and Haas Co.

Battelle

. . . Putting Technology To Work

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

Sponsor's Test Article: Ethyl Acrylate (EA) and Acrylic Acid (AA)

APPROVED, BATTELLE:

Michael J. Brooker

Michael Brooker, B.S.
Battelle Study Director

11/22/94
Date

Kathleen C. Reed

Quality Assurance

11-22-94
Date

APPROVED, SPONSOR:

Clay B. Frederick

Clay B. Frederick, Ph.D.
Project Monitor

11/28/94
Date

(Signature indicates that the activities in this protocol do not unnecessarily duplicate experiments on animal subjects.)

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

1.0 TITLE

Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA)

2.0 OBJECTIVE

The objective of this study is to evaluate the acute toxicity of AA and EA in monkeys after a single inhalation exposure.

3.0 ROUTE AND DURATION OF ADMINISTRATION

A single (either 3-hour or 6-hour) head-only inhalation exposure to one target vapor concentration of each compound; plus an air control.

4.0 SPONSOR

Rohm & Haas
727 Norristown Rd.
Spring House, PA 19477

5.0 TESTING LABORATORY

A. Facility

Battelle Columbus Division (BCD)
505 King Avenue
Columbus, Ohio 43201-2693

B. Study Team

Study Director: Mr. Michael Brooker
Study Pathologist: To be determined (TBD)
Study Clinical Pathologist: Dr. Michael Ryan
Laboratory Animal Veterinarian: Dr. Tracy Peace

6.0 TENTATIVE SCHEDULE

- Experimental Start Date: Week of 11/21/94
- Termination Date: To be determined

7.0 TEST SYSTEM

A. Species: Monkey

B. Strain: *Macaca fascicularis* (Cynomolgus)

C. Supplier: Charles River Primates, Inc.

D. Age and Sex: Young mature males and females; wild captured, exact age unknown; serologically negative for Herpes Simian B Virus

E. Weight of animals at initiation of treatment: 2-5 kg.

F. Number of animals in study: 15

G. Test System Justification: Considerable scientific documentation of the Cynomolgus monkey as a predictive animal model for humans exists. An extensive biochemical and physiological data base for the Cynomolgus monkey is available. In addition there have been numerous studies concerned with the inhalation of agents by non-human primates.

8.0 ANIMAL CARE, HOUSING, AND ENVIRONMENTAL CONDITIONS

A. Quarantine and Acceptance

1. a. The Cynomolgus monkeys (2-5 kg) have been supplied by Charles River Primates and serologically screened for a negative titer against Herpes Simian B virus prior to shipment.

   b. Within 1 week after arrival all animals were examined by a veterinarian. This included a complete physical examination, in conjunction with the first TB test and the recording of body weight.

   c. All animals received and tested negative to three sequential intradermal tuberculin tests at approximately two week intervals.

   d. At least one clinical pathology screen and fecal examination for intestinal parasites was made during quarantine. Clinical pathology screen will be repeated prior to exposure and include the following parameters.

Hematology
Erythrocyte count (RBC)
Hematocrit (HCT)
Hemoglobin (HGB)
Leukocyte cell count (WBC)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count (PLT)
WBC differential

Serum Chemistry
Alanine aminotransferase (SGPT) (ALT)
Albumin (ALB)
Alkaline phosphatase (ALP)
Aspartate aminotransferase (SGOT) (AST)
Blood urea nitrogen (BUN)
Chloride (Cl)
Creatinine (CRE)
Glucose (GLU)
Potassium (K)
Sodium (Na)
Total protein (TP)

2. The animals will be individually housed, in stainless steel, wire-bottom cages. The cage space will meet the requirements stated in the NIH "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health Publication No. 86-23), as specified by the facility standard operating procedure. All environmental conditions will conform to facility standard operating procedures (light/dark cycle, temperature, humidity, and fresh air exchanges).

3. Acceptability for Study--Animals suitable for study will be selected by the Study Director and Study Veterinarian. They will be in good physical condition based on appearance, and demonstration of normal hematology and serum chemistry values.

4. Animal Identification--Animals will be uniquely identified by tattoos in addition to cage card.

5. Animals will be accustomed to restraint and exposure procedure prior to the initiation of treatment.

B. Feed

Monkeys will be fed Purina Certified monkey Chow 5048® (approximately six-eight biscuits) twice daily during the pretest period and the study. Monkey diets will be supplemented with fresh fruit and/or other supplements. Animals will not be fed biscuits or supplements prior to dosing. No contaminants are known to be present in the feed or supplements which would interfere with or affect the results of the study. Certified analyses of the Purina Monkey Chow 5048® will be retained in the Battelle Animal Resources Facility and be available for inspection upon request.

C. Water

Water will be provided *ad libitum* except during restraint. The City of Columbus municipal water supply will be used. The quality of the water will meet the standards set by the Columbus Water Department and Ohio Environmental Protection Agency. Periodic chemical analysis and microbial analysis of the water will be performed at Lancaster Laboratories (Lancaster, PA). Results of these analyses are kept on file at Battelle. There are no suspected containments in the water which could adversely affect the results of this study.

D. Animal Randomization

Animals will be allocated to treatment groups prior to exposure. Animals will be assigned randomly to treatment groups.

9.0 TEST ARTICLE

A log of receipt and use of the Sponsor's test article will be maintained.

A. Test Article

1. Ethyl Acrylate (EA) and Acrylic Acid (AA)

2. Supplier: Sponsor or specified by the Sponsor.

3. Storage Conditions: To be specified by the Sponsor.

4. Identity, Purity and Stability of the test article will be the responsibility of the Sponsor.

10.0 AEROSOL GENERATION AND EXPOSURE SYSTEMS

A. Test Article Generation

The test articles will be generated from a liquid state. Initially an inert gas (N_2) will be entrained into the liquid phase of the test article in a closed container. The head space vapor will be drawn off and allowed to equilibrate in a central plenum before dilution and transport to the exposure units.

Test article concentrations will be monitored using an Infrared Spectrophotometer such as a Miran 980 or similar device. A multipoint calibration curve will be developed during the pretest period to monitor concentrations for each test compound.

B. Exposure System

Each animal will be placed in a head-only exposure unit designed to provide a fresh supply of the test atmosphere at an adequate flow rate to provide minimum oxygen requirements of the animal. The actual exposure system and primary containment system will be a whole-head hood with an air dam encompassing the neck of the primate. The hood will be clear allowing the animal complete visualization of his environment. The animal exposure hood will have a continuous bias flow of approximately 7 to 10 L/min. Test atmosphere will be drawn from the generator to test subjects, and the Miran Infrared Analyzer. Test atmosphere will enter near the top and be exhausted near the bottom of the helmet.

11.0 PHYSICAL AND CHEMICAL CHARACTERIZATIONS OF THE TEST ATMOSPHERE

Before the animal exposures begin, satisfactory achievement of vapor concentrations encompassing the anticipated range will be documented for the test article.

A. Pre-Study Characterization of Test Atmospheres

1. Generation and analysis of the vapor concentration will be performed to characterize the exposure systems.

2. Uniformity of dose between helmet units will be determined prestudy using the Infrared Analyzer. A single reference location will be established and all helmet locations will be compared to the reference location during pretest validation.

B. Monitoring During Animal Exposures

Concentration of test vapors will be monitored using the Infrared Analyzer at least twice per hour from the reference location as established in the pretest validation, for the duration of exposure.

C. Target Vapor Concentrations

The inhalation exposure will be designed to expose animals to a vapor of the test article. The following table lists the target vapor concentrations.

Group Number	Test Article	No. of Animals	Vapor Conc. (ppm)	Exposure Duration (Hour)
1	Air Control	3	0	6
2	EA	3	75	3
3	EA	3	75	6
4	AA	3	75	3
5	AA	3	75	6

D. Dosimetry Measurements

Venturi's will be installed in the delivery line to each exposure helmet. The measurement of the airflow through the venturi during exposure will be used to determine the total inhaled volume of air for each animal during the exposure.

12.0 EXPERIMENTAL DESIGN

Five groups of three animals each will be exposed via head-only inhalation exposure to one target concentration level of each test compound or an air control.

A. Inhalation Exposures

Each animal will receive either a single three-hour or six-hour exposure at the target dose concentration described in Section 11.0 C.

B. Clinical Observation

Clinical observations will be recorded twice (once prior and once post-exposure) on Study Day 1.

C. Body Weight

Body weight will be determined for all animals once pretest and prior to exposure on Study Day 1.

D. Necropsy and Tissue Processing

After the end of the exposures, each monkey will be anesthetized with ketamine and sodium pentobarbital and then euthanatized by exsanguination via the femoral arteries.

Immediately after death, the head will be removed from the carcass and both nasal passages will be flushed via the nasopharyngeal orifice with 100-200 mL of 10% neutral buffered formalin. After this intranasal flush, the eyes, skin, brain, lower jaw and musculature will be removed from the head and discarded. The head will be immersed in a large volume of the same fixative for at least 24 hours until further processing.

In addition, the lungs will be removed, the trachea will be cannulated and the lungs will be suspended and fixed by tracheal infusion of 10% neutral buffered formalin at 30 cm fixative pressure for at least 2 hours. After intratracheal infusion the cannula will be removed and the proximal aspect of the trachea will be tied off by string or clamped and the trachea and lungs will be stored in a large volume of the same fixative until further tissue processing. No other tissues will be saved.

All tissues will be shipped to Dr. Jack R. Harkema for sectioning and histopathological evaluation:

Michigan State University
Dept. of Pathology
A54 Veterinary Medical Center
East Lansing, MI 48824-1314
Phone: (517) 353-8627
Fax: (517) 355-2152

13.0 REPORTING

A draft report of this study will be submitted within 60 days after completion of the in-life phase. The report will include, but not be limited to the following:

- Objectives and procedures as stated in the approved protocol.
- Description of the test article generation and exposure system and the operating conditions.
- Performance of the exposure system (i.e., chemical and physical data).
- Statistical methods employed and results obtained.

- Discussion of the results.
- Deviations from the laboratory's SOPs or the approved protocol, if any.
- No data or interpretation from the histopathological evaluation will be included in the final report.

Final Report

Final report will be submitted to Sponsor within 30 days of receipt of the Sponsor's comments on the draft report.

14.0 STUDY CONDUCT, STORAGE OF STUDY MATERIALS, AND RECORDS RETENTION

This protocol will be the controlling document in case of discrepancies between the Protocol and SOPs. All remaining test articles will be returned to the Sponsor or their designated archive facility upon completion of the final report. All original records required to reconstruct the conduct of the study will be shipped to the Sponsor for archival in the Rohm & Haas archives. A copy of all data and the final report will be retained in the Battelle archives. Battelle will not retain any specimens or tissues.

15.0 STUDY CHANGES

If after the study is underway, it becomes necessary to change the approved protocol, verbal agreement to make this change will be made between the study director and the Sponsor's representative. As soon as practical, the change and reasons for it will be formally approved by the Study Director and Sponsor's representative in writing and amended to the study protocol. This document will be added to the study file.

16.0 STATISTICAL ANALYSIS

Only means and standard deviations will be reported for animal group data. No statistical comparisons will be conducted between expsoure groups.

17.0 GOOD LABORATORY PRACTICES COMPLIANCE

This study will be conducted in accordance with the U.S. Environmental Protection Agency Good Laboratory Practice (GLP) Standards (40 CFR Part 792). The study will be conducted in compliance with Battelle Standard Operating Procedures (SOPs). Maintenance and use of animals will be in accordance with the guideline contained in NIH publication 86-23 (Guide for the Care and Use of Laboratory Animals).

Study No.: SC940138

PROTOCOL AMENDMENT NUMBER 1

Effective Date: December 14, 1994

To: The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

1. Part to be Ammended: Section 5.0 B, Study Team, Page 3.

Add the following statement to the section:

Study Pathologist: Dr. Allen Singer

Reason for the Ammendment:

At the time the protocol was signed, the study pathologist had not been assigned to the study team.

APPROVED BY:

Michael J. Brooker
Study Director

2/14/95
Date

Clay B. Frederick, Ph.D., D.A.B.T.
Project Monitor

2/15/95
Date

Study No.: SC940138

PROTOCOL AMENDMENT NUMBER 2

Effective Date: March 20, 1995

To: The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

1. Part to be Amended: Section 7.0 F, Page 4.

   Change the section to read:

   Number of animals on study: 16

2. Part to be Amended: Section 12.0 Experimental Design, Page 8.

   Add Section 12.0 E. Image Analysis Animal, to the protocol:

A single animal will be used to collect image analysis data and define the parameters for tissue sectioning. This animal will not be exposed via the head-only inhalation system. The animal will be anesthetized, euthanized and the head processed as described in section 12.0 D, then wrapped in formalin soaked cotton, placed in a plastic bag and shipped. This animal will be shipped to:

Dr. Kevin Morgan
CIIT
6 Davis Drive
Research Triangle Park, NC, 27709
Phone 919-558-1297

No other tissues will be saved for this single animal. Relevant animal history data (as defined by this protocol) for this animal will be maintained in the study file.

Reason For Changes: Sponsor requested the changes be made to the protocol.

APPROVED BY:

Michael J. Brooker
Study Director

3/23/95
Date

Clay B. Frederick, Ph.D., D.A.B.T.
Project Monitor

3/29/95
Date

PROTOCOL DEVIATION REPORT

for

The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid
(Study #: SC940138)

Date of deviation: November 22, 1994

Nature of deviation:

Two animals did not conform to the standards described in the protocol in Section 8.0 A, Quarantine and Acceptance.

Cause of deviation:

Animals #30-544 and #30-537 received a physical examination 10 days after arrival which was not in the first week after arrival as stated in the protocol.

Impact on the Study:

None.

Corrective action:

Protocol Deviation added to study file.

Approved by: Michael J. Brewer Date: 3/24/95
Study Director

Distribution: Study file (original)

PROTOCOL DEVIATION REPORT

for

Single Dose Inhalation Toxicity
Study of Ethyl Acrylate and Acrylic Acid

(Study #: SC940138)

Date of deviation: 12/14/94, 12/21/94

Nature of deviation:

Two animals were outside of the protocol specified weight range on their respective exposure day.

Cause of deviation:

Animals were slightly larger than anticipated when the weight range was defined.

Impact on the study:

None. Animals were weighed as required by the protocol and the total inhaled dosages were calculated based on the current animal body weight.

Corrective action:

None.

Approved by: Michael J. Brooker Date: 2/1/95
Study Director

Distribution: Study file (original)

PROTOCOL DEVIATION REPORT

for

The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid
(Study #: SC940138)

Date of deviation: December 13 and 16, 1995

Nature of deviation:

Three animals did not conform to the standards described in the protocol in Section 7.0 D, Age and Sex.

Cause of deviation:

Animals 30-537, 30-544, and 122-55 tested positive for Herpes B virus.

Impact on the Study:

None.

Corrective action:

Protocol Deviation added to study file along with documentation of test results.

Approved by: Michael J. Brock Date: 2/15/95
Study Director

Distribution: Study file (original)

APPENDIX B

MIRAN 980 CALIBRATION DATA

Table B-1. Individual Data Points for the Miran 980 Calibration with Ethyl Acrylate for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Injection Amount (μL)	Calculated Conc. (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.
0	0	0.0013	-0.0002	0.0007	0.0007	0.0004
0	0	0.0011	0.0018	0.0015	0.0020	0.0018
0	0	0.0014	0.0019	0.0023	0.0019	0.0020
0.5	19.5	0.0020	0.3202	0.3204	0.3206	0.3204
0	0	0.0009	0.0014	0.0021	0.0016	0.0017
0.5	19.5	0.0020	0.3189	0.3203	0.3201	0.3198
0	0	0.0010	0.0007	0.0010	0.0009	0.0009
0.5	19.5	0.0020	0.3122	0.3127	0.3125	0.3125
0	0	-0.0001	-0.0057	-0.0056	-0.0056	-0.0056
1	39	0.0013	0.5028	0.5036	0.5024	0.5029
0	0	0.0002	-0.0055	-0.0052	-0.0052	-0.0053
1	39	0.0024	0.5079	0.5076	0.5085	0.5080
0	0	0.0007	-0.0054	-0.0047	-0.0051	-0.0051
1	39	0.0029	0.5054	0.5062	0.5063	0.5060
0	0	0.0010	0.0037	0.0041	0.0038	0.0039
2	78	0.0051	0.6808	0.6805	0.6815	0.6809
0	0	0.0012	-0.0006	0.0004	-0.0001	-0.0001
0	0	0.0014	-0.0021	-0.0013	-0.0017	-0.0017
2	78	0.0050	0.6835	0.6852	0.6853	0.6847
0	0	0.0012	-0.0008	-0.0007	-0.0010	-0.0008
2	78	0.0058	0.6817	0.6833	0.6825	0.6825
0	0	0.0016	-0.0037	-0.0034	-0.0035	-0.0035
3	117	0.0075	0.7979	0.7984	0.8002	0.7988
0	0	0.0012	0.0014	0.0023	0.0017	0.0018
3	117	0.0076	0.7953	0.7955	0.7960	0.7956
0	0	0.0020	-0.0032	-0.0023	-0.0030	-0.0028
3	117	0.0076	0.8031	0.8012	0.8007	0.8017
0	0	0.0024	-0.0047	-0.0044	-0.0047	-0.0046
3	117	0.0083	0.8053	0.8021	0.8031	0.8035
0	0	0.0021	-0.0052	-0.0048	-0.0047	-0.0049

Table B-2. Individual data points for the Miran 980 calibration with Acrylic Acid for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Injected Amount (μL)	Calculated Conc. (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.
0	0	-0.0001	0.0004	0.0009	0.0000	0.0004
0	0	0.0002	0.0009	0.0012	0.0006	0.0009
0	0	0.0001	0.0009	0.0007	0.0009	0.0008
0	0	-0.0001	0.0011	0.0012	0.0013	0.0012
0.25	15.8	0.0008	0.0979	0.0977	0.0974	0.0977
0	0	0.0002	0.0034	0.0038	0.0037	0.0036
0.25	15.8	0.0012	0.1050	0.1049	0.1046	0.1048
0	0	0.0009	-0.0002	-0.0001	0.0000	-0.0001
0.25	15.8	0.0028	0.0956	0.0961	0.0956	0.0958
0	0	0.0006	0.0005	0.0006	0.0005	0.0005
0.5	31.6	0.0051	0.1984	0.1978	0.1969	0.1977
0	0	0.0012	0.0037	0.0040	0.0039	0.0039
0.5	31.6	0.0055	0.2102	0.2091	0.2094	0.2096
0	0	0.0015	0.0010	0.0010	0.0011	0.0010
0.5	31.6	0.0053	0.2041	0.2039	0.2040	0.2040
0	0	0.0006	0.0001	-0.0005	-0.0004	-0.0003
1	63.2	0.0120	0.3517	0.3511	0.3506	0.3511
0	0	0.0012	-0.0045	-0.0041	-0.0046	-0.0044
1	63.2	0.0124	0.3511	0.3515	0.3513	0.3513
0	0	0.0012	-0.0039	-0.0035	-0.0042	-0.0039
1	63.2	0.0124	0.3574	0.3567	0.3556	0.3566
0	0	0.0012	-0.0045	-0.0044	-0.0045	-0.0045
2	126.4	0.0408	0.5740	0.5750	0.5737	0.5742
0	0	0.0012	-0.0017	-0.0010	-0.0014	-0.0014
2	126.4	0.0401	0.5740	0.5728	0.5739	0.5736
0	0	0.0009	-0.0051	-0.0051	-0.0055	-0.0052
2	126.4	0.0389	0.5702	0.5685	0.5699	0.5695

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Volume 36, No. 1, Part 2,
March 97

576 OLFACTORY EPITHELIAL INJURY IN MONKEYS AFTER ACUTE INHALATION EXPOSURE TO ACRYLIC MONOMERS.

J R Harkema[1], J K Lee[1], K T Morgan[2], and C B Frederick[3]. [1]*Department of Pathology, Michigan State University, East Lansing, MI;* [2]*Chemical Industry Institute of Toxicology, Research Triangle Park, NC; and* [3]*Rohm and Haas Co., Spring House, PA.*

Inhalation exposures of acrylic monomers induce toxic responses in the nasal olfactory epithelium of rodents, but such effects have not been investigated in other species. The purpose of the present study was to determine the effects of inhaled ethyl acrylate (EA) and acrylic acid vapors (AA) on the nasal epithelium of monkeys. Cynomolgus monkeys were exposed to 0 (filtered air) or 75 ppm EA or AA for 3 or 6 h (3 animals/exposure group). The nasal cavity from each monkey was processed for light microscopic analysis. The nose was cut in a series of transverse sections extending from the nares to the nasopharynx. Diagrams of the transverse airway profiles were used to map the distribution of exposure-related lesions. The severity of lesions was estimated using standard morphometric techniques. EA- and AA-induced lesions were restricted to the olfactory epithelium lining the dorsal medial meatus. Both EA and AA caused focal degeneration, necrosis, and exfoliation of the olfactory epithelium with mild inflammation. Lesion distribution and severity were greater in animals exposed for 6 h compared with those in monkeys exposed for 3 h. Approximately 15% and 50% of the olfactory epithelium had EA- or AA-induced damage after 3 and 6 h, respectively. The results of this study indicate that monkeys exposed to EA or AA have focal, olfactory epithelial lesions that resemble, in both nature and severity, those previously reported in rodents. (Research was supported by the Basic Acrylic Monomer Manufacturers.)

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C-002

American Chemistry Council

Attachment 25

June 1, 2001

Via Hand Delivery

OPPT Document Control Office
United States Environmental Protection Agency
East Tower
Room G-099
Waterside Mall
401 M Street, S.W.
Washington, D.C. 20460

Re: Notice Concerning the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Proposed AEGL Values for Phenol, 66 Fed. Reg. 21940 (May 2, 2001); OPPTS-00312

Dear OPPT Document Control Office:

The Phenol Regulatory Panel (Panel) of the American Chemistry Council submits the appended comments on the United States Environmental Protection Agency's proposed acute exposure guideline levels for phenol. The Panel is comprised of domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical.

Please direct any questions concerning these comments to Mr. Jonathon T. Busch, Manager of the Phenol Regulatory Panel, at (703) 741-5633.

Sincerely yours,

Jon Busch

Attachment

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BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMMENTS OF THE AMERICAN CHEMISTRY COUNCIL'S PHENOL REGULATORY PANEL ON THE NATIONAL ADVISORY COMMITTEE FOR ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR HAZARDOUS SUBSTANCES PROPOSED AEGL VALUES FOR PHENOL

Notice Concerning the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Proposed AEGL Values for Phenol, 66 Fed. Reg. 21940 (May 2, 2001).	OPPTS – 00312 FRL – 6776-3

Courtney M. Price
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1300 Eye Street, N.W.
Suite 1000 West
Washington, D.C. 20005

June 1, 2001

AMERICAN CHEMISTRY COUNCIL
1300 Wilson Boulevard
Arlington, VA 22209
(703) 741-5000

EXECUTIVE SUMMARY

The American Chemistry Council's Phenol Regulatory Panel (Panel) submits these comments on the U.S. Environmental Protection Agency's (EPA) proposed acute exposure guideline levels (AEGLs) for phenol, published in the *Federal Register* on May 2, 2001. 66 Fed. Reg. 21940, 21952-4. The Panel is comprised of domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical.

The Panel urges the NAC/AEGL Committee to revise the proposed AEGL-3 and AEGL-2 values for phenol and adopt significantly higher values for the following reasons:

- The Panel urges the NAC/AEGL Committee to adopt AEGL-3 values that are no lower than the 1-hour level Emergency Response Planning Guideline, Level 3 (ERPG-3) of 200 ppm, established by the American Industrial Hygiene Association (AIHA), with appropriate time scaling for different exposure periods, for the following reason:

  - It is reasonable to assume that the lethal or life-threatening endpoints of concern in an AEGL-3 determination occur at a substantially higher dose than was administered for 8 hours in the rat study relied upon for calculating the AEGL-3 values -- the Flickinger study.

  - The proposed AEGL-3 value of 23 ppm for 8 hours of exposure is on its face scientifically unsound and inappropriate given that, in the CMA (1998) study, rats exposed to 25 ppm for 6 hours/day for 10 days exhibited no adverse effects.

  - While it is highly questionable whether estimated exposure levels in the human reports cited in the AEGL Support Document as corroboration for the proposed AEGL-3 values are sufficiently accurate even for use as corroborative data, to the extent they are utilized, they support application of an uncertainty factor to the Flickinger study considerably smaller than the ten-fold uncertainty factor assumed in establishing the AEGL-3 values.

  - The 10-minute AEGL-3 value should be derived by applying the time-scaling equation in the same manner the equation was used to derive values for other time periods.

- The proposed AEGL-2 values for phenol are based on unreasonable assumptions and methodology and accordingly also are substantially too low.

  - The endpoints observed in the Flickinger study do not clearly meet the AEGL-2 criteria.

- Application of an *intraspecies* variability uncertainty factor of 3 to the Flickinger study, rather than the 10-fold *intraspecies* uncertainty factor used in the Support Document, and therefore application of a 9- to 10-fold *overall* uncertainty factor, rather than the 30-fold uncertainty factor assumed in the Support Document, are justified on several grounds. These include, among other considerations, the fact that in the well-conducted multiple dose, multiple exposure study by CMA (1998), no adverse effects were observed in rats administered 25 ppm phenol 6 hours/day, 5 days/week for 2 weeks (the highest dose administered).

- While the CMA study is a superior study, with multiple doses, because it has a free-standing no observed adverse effect level for adverse effects, use of the Flickinger study after applying an *overall* 9- to 10-fold uncertainty factor is warranted.

- The 10-minute AEGL-2 value should have been derived by applying the time-scaling equation in the same manner the equation was used to derive values for other time periods.

TABLE OF CONTENTS

INTRODUCTION

The American Chemistry Council's Phenol Regulatory Panel (Panel) submits these comments on the U.S. Environmental Protection Agency's (EPA) proposed acute exposure guideline levels (AEGLs) for phenol, published in the *Federal Register* on May 2, 2001. 66 Fed. Reg. 21940, 21952-4. The Panel is comprised of domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical.[1]

I. THE PROPOSED AEGL-3 VALUES FOR PHENOL ARE BASED ON UNREASONABLE ASSUMPTIONS AND METHODOLOGY AND ACCORDINGLY ARE SUBSTANTIALLY TOO LOW

The Panel urges the NAC/AEGL Committee to revise the proposed AEGL-3 values for phenol and adopt values that are no lower than the 1-hour level Emergency Response Planning Guideline, Level 3 (ERPG-3) of 200 ppm, established by the American Industrial Hygiene Association (AIHA) with appropriate time scaling for different exposure periods. The ERPG-3 is intended to be based on essentially the same criteria that are used to establish the AEGL-3.[2] Alternatively, the Panel suggests the NAC/AEGL Committee consider concluding that the database is insufficient to derive AEGL-3 values and therefore decline to do so.

---

[1] Panel members include: Aristech Chemical Corporation; Dakota Gasification Company; The Dow Chemical Company; Fenoquimia, S.A. de C.V.; General Electric Corporation; Georgia Gulf Corporation; JLM Industries, Inc.; Merisol Company (Merichem-Sasol USA LLC); Phenolchemie Inc.; Shell Chemical Company; and Sunoco Inc. Associate members are: BF Goodrich; Borden Inc.; and The Procter & Gamble Company.

[2] The AEGL-3 is defined as the "airborne concentration. . . . of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death." 66 Fed. Reg. at 21941. The ERPG-3

AIHA based the ERPG-3 on the Flickinger study in rats,[3] as did the NAC/AEGL Committee. In the Flickinger study, rats exposed to 234 ppm phenol exhibited ocular and nasal irritation, muscle spasms, and slight loss of coordination after 4 hours of exposure. One of the six rats tested exhibited tremors and prostration after 8 hours of exposure.

None of these effects properly may be characterized as lethal or life-threatening, the endpoints of concern in an AEGL-3 determination. Indeed, it is highly questionable that these effects satisfy the criteria for AEGL-2 or ERPG-2 effects,[4] given that the rats appeared normal the following day, had normal 14-day weight gains, and exhibited no lesions attributable to inhalation of the phenol at gross autopsy.[5] Therefore, it is reasonable to assume that the AEGL-3 endpoint occurs in rats at a substantially higher dose than was administered in the Flickinger study after 8 hours of exposure.[6]

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is defined as the "maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects." EPA, Phenol (CAS Reg. No. 108-95-2) Proposed Acute Exposure Guideline Levels (AEGLs), "Public Draft," Proposed 1:2/2001 at 39 (Support Document).

3 Flickinger, C.W. (1976). "The benzenediols: catechol, resorcinol and hydroquinone – a review of the industrial toxicology and current industrial exposure limits." *Am. Ind. Hyg. Assoc. J.* 37:596-606.

4 These criteria are described below.

5 Support Document at 15-16; Flickinger (1976).

6 The Support Document also should make clear that the Brondeau, *et al.* (1990) study confirms that the levels of phenol administered in the Flickinger study do not elicit significant adverse effects meeting the AEGL-3 criteria.

A number of other considerations indicate that the proposed AEGL-3 values are substantially too low:

- It is scientifically unsound to establish an AEGL-3 value, which is intended to indicate the strong potential for lethality after up to 8 hours of exposure in a single day, at a level similar to a level that induced no adverse effects in laboratory animals after multiple days of exposure. For example, the proposed AEGL-3 value of 23 ppm for 8 hours of exposure is on its face inappropriate given that in the CMA (1998) study, rats exposed to 25 ppm for 6 hours/day for 10 days exhibited no adverse effects.

- The Support Document inappropriately utilizes case studies reporting lethal effects in humans after ingestion of phenol in justifying application of a 10-fold uncertainty factor, rather than a smaller uncertainty factor, to the exposure level in the Flickinger study. The Support Document indicates that the calculated AEGL-3 values for the various time periods, from 30 minutes to 8 hours, were 8-fold to 48-fold lower than the lower boundary of the estimated dose range of the reported lethal cases after oral and dermal exposure.[7] The lower boundary estimates for the human lethality cases, however, are based on the lower end of tissue concentration measurements, which showed a wide range in each subject where exposure levels were estimated in that manner.

  This is a highly unreliable method of estimating exposure levels as the variation in these data are likely derived from differences in the analytical techniques used to measure phenol in human tissue, as well as the variability in reporting of the dose or exposure of phenol which occurred in these human poisonings, rather than intraspecies variation in metabolism or pharmacokinetics. Indeed, pharmacokinetic studies conducted on phenol have shown very good animal-to-animal reproducibility in the data (Hiser *et al.*, 1994; Piotrowski, 1971, *Br. J. Ind. Med.* 28: 172-178). The few case reports where the intake appeared to be known with more certainty indicated intakes two and a half to six-fold higher than the lower boundary assumed in the report, and these levels were all above the exposure level in the Flickinger study. In addition, the manner in which the human reports are used does not take into account that the ingestions occurred as a single incident, resulting in absorption of the phenol into the body over a short period of time. Therefore, the peak blood concentrations or estimated delivered doses in effect were somewhat higher than if the exposures occurred over several hours as

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[7] *See* Support Document at 33-34.

phenol is rapidly and completely absorbed following an oral bolus dose (Gingell *et al.*, 2000)[8].

In sum, while it is highly questionable whether estimated exposures for the human reports are sufficiently accurate even for use as corroborative data, to the extent they are utilized, they support application of an uncertainty factor to the Flickinger study considerably smaller than the ten-fold uncertainty factor assumed in establishing the AEGL-3 values.

- The 10-minute AEGL-3 value should be derived by applying the time-scaling equation in the same manner the equation was used to derive values for other time periods. The Support Document does not provide adequate justification for using the same AEGL-3 value for both 30-minute and 10-minute exposures. The explanation provided by the Support Document for using the time-scaling equation in deriving the 10-minute AEGL-1 value also applies to the derivation of the 10-minute AEGL-3 value.[9] The use of an n = 3 value in the time scaling $C^n \times t = k$ equation, however, may also be inappropriate as the AEGL-3 8-hour value produced is inconsistent with the CMA (1998) study results where rats exposed to 25 ppm for 6 hours/day for 10 days exhibited no adverse effects.

It appears that human and animal data sufficient to reliably estimate the exposure level that meets the AEGL-3 criteria are lacking. Alternatively, the Panel suggests that the NAC/AEGL Committee consider concluding that the database is insufficient to derive AEGL-3 values and therefore decline to do so.

II. THE PROPOSED AEGL-2 VALUES FOR PHENOL ARE BASED ON UNREASONABLE ASSUMPTIONS AND METHODOLOGY AND ACCORDINGLY ALSO ARE SUBSTANTIALLY TOO LOW

The Support Document indicates that the proposed AEGL-2 values were derived from the CMA (1998) study, which had several test groups and a free-standing no observed

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8 Patty's Toxicology: Gingell, R. et al. "Phenol and Phenolics." John Wiley & Sons, Inc. Volume 4, Fifth Edition, Chapter 53, Pages 383-551, 2001

adverse effect level (NOAEL) of 25 ppm. The Support Document further indicates that the proposed AEGL-2 values were corroborated by deriving similar, but slightly higher, AEGL-2 values from the Flickinger study.[10] The Panel recommends that the AEGL-2 values be based on the Flickinger study, but only after application of a total uncertainty factor of 9 or 10, rather than the 30-fold uncertainty factor applied by the NAC/AEGL Committee to that study. Because the CMA (1998) study indicates no adverse effects, that study should be used to corroborate application of a much smaller uncertainty factor to the Flickinger study. This recommendation is based on several considerations.

First, the endpoints observed in the Flickinger study do not clearly meet the AEGL-2 criteria. Those criteria define AEGL-2 as the airborne concentration of a substance "above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape."[11] As discussed above, the test animals were all normal the day after the exposure. Accordingly, the study does not indicate irreversible or other serious, long-lasting adverse health effects. Moreover, the muscle spasms and slight loss of coordination that were reported are not sufficiently severe to result in an impaired ability to escape. Further, the fact that tremors and prostration were observed in only one of six mice, makes questionable the inference that such effects were induced by the test substance.

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9 *See* Support Document at 29.

10 Support Document at 30-31.

11 66 Fed. Reg. at 21941.

Application of an *intraspecies* variability uncertainty factor of 3 to the Flickinger study, rather than the 10-fold *intraspecies* uncertainty factor used in the Support Document, is justified on the following grounds:

- The Flickinger study reported effects that were below the AEGL-2 criteria, or at worst, that barely meet the criteria in only a single animal.
- As recognized by the Support Document, "available human data do not point at a large intraspecies variability."[12]
- In the well-conducted multiple dose, multiple exposure study by CMA (1998), no adverse effects were observed in rats administered 25 ppm phenol 6 hours/day, 5 days/week for 2 weeks (the highest dose administered).

This 3-fold factor, combined with the 3-fold interspecies uncertainty factor assumed in the Support Document, results in an overall uncertainty factor of 9 to 10 to be applied to the Flickinger study. While the CMA study is a superior study, with multiple doses, because it has a free-standing NOAEL for adverse effects, use of the Flickinger study after applying an overall 9- or 10-fold uncertainty factor is warranted.

Further, the 10-minute AEGL-2 value should have been derived by applying the time-scaling equation in the same manner the equation was used to derive values for other time periods. The Support Document provides inadequate justification for using the same AEGL-2 value for both 30-minute and 10-minute exposures. The explanation provided by the Support

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12 Support Document at 29.

document for using the time-scaling equation in deriving the 10-minute AEGL-1 value also applies to the derivation of the 10-minute AEGL-2 value.[13]

Alternatively, the Panel suggests that the NAC/AEGL Committee consider concluding that the database is insufficient to derive AEGL-2 values and therefore decline to do so.

CONCLUSION

The Panel appreciates the opportunity to comment on the proposed AEGL values for phenol. The Panel urges the NAC/AEGL Committee to revise the AEGL values and the Support Document consistent with these comments.

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[13] *See* Support Document at 29.

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Methanol Institute

Phone: 202 467-5050
Fax: 202 331-9055

May 25, 2001

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Attachment 26

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OPPT CBIC

Ms. Barbara Cunningham, Acting Director
Environmental Assistance Division (7401)
Office of Pollution Prevention and Toxics
Environmental Protection Agency (EPA)
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Docket Control No. OPPTS-00312 – Acute Exposure Guideline Levels (AEGL) for Methanol (CAS No. 67-56-1)

Dear Ms. Cunningham:

This letter responds to the May 2, 2001, announcement in the Federal Register (Vol. 66, No. 85) concerning the efforts by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) to develop Acute Exposure Guideline Levels (AEGLs) for Methanol (CAS No. 67-56-1). We understand that AEGLs are developed to provide federal, state and local agencies with information on short-term exposure to potentially hazardous chemicals and welcome the opportunity by the U.S. Environmental Protection Agency (EPA) to review and comment on the established AEGL values.

The Methanol Institute (MI) and its member companies have reviewed extant data and compared the proposed AEGL values to methanol exposure standards established by various governmental agencies in several countries including the United States, Canada, Germany and the Netherlands.

It is our opinion that the AEGL levels proposed by the NAC/AEGL Committee are consistent with similar standards found in other countries. Therefore, the Methanol Institute wishes to express its categorical support of the AEGL values proposed by the national Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Committee. If the proposed AEGL for methanol should change as the proposal works it way through the process, the Methanol Institute will re-evaluate its support.

It is extremely important for our industry to be engaged and supportive with the EPA throughout its evaluation process on methanol, as already evidenced by our participation in the EPA HPV process and the Integrated Risk Information System (IRIS) evaluation process. We will continue to assist all agencies and provide whatever data and information is needed to carry out initiatives and produce the most thorough assessments possible on our product.

Please do not hesitate to contact me or Bailey Condrey, Methanol Institute Communications Director, if you have any questions or would like further information. The main number of the Methanol Institute is (202) 467-5050.

We look forward to working with you and other staff members throughout the methanol evaluation process.

Sincerely,

Contain NO CBI

John Lynn
President & CEO

800 Connecticut Avenue, NW, Suite 620• Washington, DC 20006• E-mail: MI@methanol.org• Internet: www.methanol.org

Attachment 27

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460

June 1, 2001

Docket control # OPPTS-00312: Methanol AEGL 1 and 2 values

I would like to raise two concerns regarding the AEGL values recommended by the AEGL Committee for methanol. The committee should be aware that this chemical is released in significant amount to the environment (192 million pounds in 1998 as air releases: TRI data).

For the AEGL-1 level, the committee has recommended that an uncertainty factor of 3 be applied when extrapolating from a finding of no adverse outcome (Batterman study) to arrive at the recommended 8 hour value. The basis of this is an email communication by an investigator of their memory of what study subjects said to him in a casual conversation 4 years earlier. It should be noted that demographics are presented on only 4 of 27 participants in the study. These four were age 41-63 while all subjects were nonsmokers. Although of interest and worth noting in the TSD it's quality should be taken into account when relying on it to extrapolate back to other values. The committee relied on this value to extrapolate back to a 30 minute value of 670 ppm. If the uncertainty factor of 3 is protective, there should be no evidence of effects below a value three times the 30 minute value. This would mean that an exposure of 2,010 ppm for 30 minutes should be a threshold of AEGL-1 effects. A NIOSH HHE report (1981-177, 178-988), however, reports that "the operator experienced eye irritation during the sampling period" which was at a measured level of 1,025 ppm methanol for 25 minutes.

This is also supported by the Kawai 1991 study. The high exposed group reported 50% dimmed vision when compared to a low exposed group (0%); 11 of the 22 workers in the high group. Their mean exposure was 459 ppm (upper range around 5,500 ppm). Even if this symptom is attributed to those workers with the highest exposure, the lowest level that all 11 would have to be exposed to is approximately 1,200 ppm for 8 hours (Figure 3 includes the exposure level for 33 high and low exposed workers). It is more likely that at least one of these workers experienced the symptom at a lower level, which would further lower the threshold for this symptom. In either case, this is supportive evidence that levels around 1,200 ppm can produce AEGL-1 health effects (dimmed vision). This is consistent with the AEGL SOP - Elements for the Evaluation of Data and Studies which states "identifying the lowest does at which it (the effects) is seen for each AEGL severity level strengthens the confidence in the study" (point 18, page 38).

Therefore the Committee's recommended 30 minute AEGL-1 value does not afford the protection of an uncertainty factor of 3. In addition there have been substantial revisions of the draft document since the committee's deliberations. With the new TSD and more accurate descriptions of some studies, I would hope the committee would reconsider the AEGL-1 value. Alternatives are setting the AEGL-1 value at: 1)

270 ppm for all time ds or 2) starting from the 1,025 ppm value for 25 minutes found by NIOSH (supported by Kawa nmed vision at 1,200 ppm), dividing by 3 for human variability and extrapolating to lon ne periods.

A recent report by PA of May 2, 2001 contains comments that are relevant to the Committee's AEGL-2 value, spec y related to adverse reproductive outcomes from the (Federal Register: May 2, 2001; pages 21929 -0). This describes the "Reproductive and Offspring Developmental Effects Following Inhalatic posure to Methanol in Nonhuman Primates"; Burbacher et al, 1999; Health Research Report N er 89 and concludes:

"Taken together, tudies of Rodgers et al and Burbacher et al provide a pattern of evidence indicative of reproductive a velopmental toxicity associated with exposure of mice and monkeys to methanol vapor during ges . In our judgment, this evidence is relevant for evaluating potential risks of methanol to hum ealth."

I request that th mmittee examine this report and determine if their findings lower the current recommended A -2 levels.

John S. Morawe

c: Fra D. Martino
Secretary Treasurer's Office
Eric Bray
Micnael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Rodger Garrett, EPA

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances

Final Meeting 20 Highlights

U. S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D.C.
January 8-10, 2001

INTRODUCTION

Welcoming remarks were provided by George Rusch (NAC/AEGL Chairperson) and George Cushmac (meeting host, Department of Transportation). The Highlights of the NAC/AEGL Meeting 19 were reviewed and discussed. With regard to approval of the discussion in the minutes concerning the nerve agents GA, GB, GD, GF, and Agent VX, a question was raised by Robert Snyder. He questioned whether the committee had decided to treat the G Agents similar to Agent VX in that the AEGL values would be agreed to for a period of three years, after which the committee would revisit the values and decide if–in the light of any new data–the values should be reconsidered. Bob Snyder agreed to review the NAC/AEGL-19 tapes for discussion content and report back at the next NAC/AEGL meeting. Mark McClanahan made a motion for Bob to review the tapes and approve the meeting highlights excluding pages of meeting highlights pertinent to the development of AEGLs for G agents and VX and was seconded by George Rodgers. Then, the NAC/AEGL-19 highlights will be revised accordingly (Appendix A). The motion passed [YES: 21; NO: 0; ABSTAIN: 2] (Appendix B).

Roger Garrett, AEGL Program Director, announced and invited all in attendance to the U.S. EPA Awards Ceremony at the NAS Auditorium following the afternoon adjournment.

The highlights for the NAC/AEGL-20 are presented below and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

GENERAL INTEREST ITEMS

Federal Register Notices submitted for comment in December 2000 were not received by the time of NAC/AEGL Meeting 20. When comments are received telephone conferences will be conducted to address any significant comments and any changes will be voted upon by telephone conference. Note: NAC/AEGL approved the following chemicals: Ethyleneimine, Propylenimine, Methacrylonitrile, Isobutylnitrile, Proprionitrile, and Chlorine trifluoride.

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

Phenol, CAS Reg. No. 108-95-2

Chemical Manager: Robert Snyder, Rutgers University
Chemical Manager: Ursula Gundert-Remy and Juergen Pauluhn, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented an overview of the Technical Support Document (Attachment 3) which contained very little quantitative inhalation data for humans. An odor threshold was set at 0.06 ppm (AIHA, 1989). Piotrowski (1971) did not report on effects in a toxicokinetic study, in which subjects were exposed to 1.3-6.5 ppm for 8 hours. Likewise, Ogata et al. (1974) in a toxicokinetic field study did not mention any effects on workers exposed to a TWA 1.22-4.95 ppm. Animal studies included continuous exposure of rhesus monkeys, rats and mice to 5 ppm phenol for 90 days, which did not cause effects (Sandage, 1961). After exposure of rats to 0.5, 5, and 25 ppm for 6 h/d, 5 d/w for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998). However, red nasal discharge was reported mostly in males and increased in occurrence from the first to the second week.

It was proposed by Steve Barbee that the AEGL-3 be established first. Robert Snyder moved and seconded by Robert Benson that Committee accept the values as proposed and obtained from the Flickinger (1976) study, in which exposure of rats to a phenol aerosol concentration of 900 mg/m³ phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in tremors, incoordination in all and prostration in 1 of 6 animals, but not in death. Time extrapolation was done according to the Standard Operating Procedures (SOP) (n=3 for shorter exposure periods up to 30 minutes; the value for 30 minutes was used for 10 minutes without further changes). The total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was based on comparison of the dose equivalent to the derived AEGL-3 values with reports on lethal and non-lethal effects in humans after oral uptake of phenol. The AEGL-3 values were approved [YES: 17; NO: 4; ABSTAIN:0] (Appendix C).

The AEGL-2 values were proposed using the CMA (1998) study, which reported a NOAEL in rats of 25 ppm phenol (highest concentration used) for 6 h/d, 5 d/w for 2 weeks. Time extrapolation was done according to the SOP (n=1 from 6 to 8 hours; n=3 for shorter exposure periods up to 30 minutes; the value for 30 minutes was used for 10 minutes without further changes). A total uncertainty factor of 3 (interspecies: 1; intraspecies: 3) was used because the exposure concentration used was a no-observed-adverse-effect-level in a repeated exposure study. A motion was made by Bob Snyder and seconded by Richard Thomas to accept the proposed values with exception of the 10-minute value. These are: 19, 15, 9.5, and 6.3 ppm for 30 minutes, and 1-, 4- and 8 hours, respectively. The motion passed. [YES: 19; NO: 2;

ABSTAIN: 2] (Appendix C). Following further discussion, Robert Benson moved that the 10-minute value be set equal to the 30-minute value which was 19 ppm. John Hinz seconded and it was approved [YES: 18; NO: 5; ABSTAIN: 0] (Appendix C).

The Committee considered the CMA (1998) study appropriate to establish the AEGL-1 values. In this study no clinical, hematological or histopathological effects were observed in rats after exposure to 25 ppm phenol (highest concentration used) for 6 h/d, 5 d/w for 2 weeks. The Committee discussed the relevance of the endpoint red nasal discharge in rats, found in male rats in the CMA (1998) study, and regarded it as a minor, but not relevant effect. Time extrapolation was done according to the SOP (n=1 from 6 to 8 hours; n=3 for shorter exposure periods up to 10 minutes; extrapolation to the 10-minute period was done because data were available for the RD_{50} value in mice). A total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was used because a multiple exposure study was used and the study reported no effects and thus was below the AEGL-1 effect level. Thomas Hornshaw moved and Richard Niemeier seconded that the Committee accept the proposed AEGL-1 values as 8.3, 5.7, 4.5, 2.9, and 1.9 ppm for 10 minutes, 30 minutes, and 1-, 4-, and 8-hours, respectively. This motion carried [YES: 18; NO: 4; ABSTAIN: 0]. (Appendix C)

There was additional comment that the TSD Table should state that dermal exposure can be as severe as oral or inhalation exposure.

☞**Action Item**: Larry Gephart agreed to provide an update at the next meeting on the relevance/use of RD_{50} values (concentrations that decrease the respiratory rate by 50%) for the derivation of AEGL values.

SUMMARY OF PROPOSED AEGL VALUES FOR PHENOL					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	8.3 ppm (32 mg/m^3)	5.7 ppm (22 mg/m^3)	4.5 ppm (17 mg/m^3)	2.9 ppm (11 mg/m^3)	1.9 ppm (7.3 mg/m^3)
AEGL-2	19 ppm (73 mg/m^3)	19 ppm (73 mg/m^3)	15 ppm (58 mg/m^3)	9.5 ppm (36 mg/m^3)	6.3 ppm (24 mg/m^3)
AEGL-3	59 ppm (230 mg/m^3)	59 ppm (230 mg/m^3)	47 ppm (180 mg/m^3)	29 ppm (110 mg/m^3)	23 ppm (88 mg/m^3)

Carbon Monoxide, CAS Reg. No. 630-08-0

Chemical Manager: George Rodgers, AAPCC
Chemical Manager: Hans-Uwe Wolf and Juergen Pauluhn, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented the existing pertinent data for possible AEGL values (Attachment 4). Comments immediately centered on a possible concern for children. Peter Griem informed the Committee the levels would be higher in younger people due to inhalation volumes and their smaller sizes. He also informed the Committee that the proposed AEGL-1 values would be at or below present ambient air levels. It was moved by Jonathan Borak and seconded by Mark McClanahan to *not* recommend AEGL-1 values. This motion passed [YES; 22; NO: 1; ABSTAIN: 0]. (Appendix D)

Human data relevant to establishment AEGL-2 values was discussed. Human adults with CAD (coronary artery disease) constitute a sensitive sub-population for the effects of CO. In an experimental study in patients with CAD, a level of 4% COHb (carboxyhemoglobin) concentration caused a reduced time until onset of angina (chest pain) and changes in the electrocardiogram (ST-segment depression of 1 mm or greater) during physical exertion (Allred et al., 1989; 1991). An exposure level of 4% COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. In experimental studies, an increase in the frequency of ventricular arrhythmias have been observed at COHb of 5.3%, but not at 3.7% (Sheps et al., 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3% and 5% COHb (Dahms et al., 1993). The Committee discussed the interindividual variability of the exposure conditions necessary to reach the desired COHb level as reported in these studies. Children were thought to be exposed to greater amounts of CO than adults because due to the higher ratio of minute volume to body size, COHb concentrations rise more rapidly in children than in adults. CO exposure can cause acute neurotoxic effects in children and a threshold for the end-point of syncope at 24.5% COHb was reported (Crocker and Walker, 1985) while symptoms such as headache, nausea, dizziness and dyspnea were found at a mean COHb concentration of 7.0% (Klasner et al., 1998). Long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children have also been reported (Klees et al., 1985). Using the studies of Allred et al.(1989 a, b; 1991) and Sheps et al. (1990, 1991), a COHb concentration of 4% was used as the basis for AEGL-2 derivation.
A mathematical model by Coburn, Forster, and Kane (CFK model) (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb concentration of 4% at the end of exposure periods of 10- and 30 minutes and 1-, 4- and 8 hours. A total uncertainty factor of 1 (intraspecies: 1) was used because the derivation was based on the most susceptible human sub-population (patients with coronary artery disease).
A motion was made by Judy Strickland and seconded by Loren Koller to accept the AEGL-2 values presented by Peter Griem [YES: 21; NO: 1; ABSTAIN: 0]. This motion passed (Appendix D).

Human data were also discussed for the AEGL-3. Several case reports indicate that in patients with CAD, CO exposure can contribute to myocardial infarction. Anecdotal case reports were discussed but were not considered an adequate basis for the derivation of AEGL-3 values because of uncertainties in the end-of-exposure COHb concentration and the insufficient characterization of the exposure conditions (with repeated and/or prolonged exposures in several cases). Therefore, the experimental studies of Chiodi et al. (1941) and Haldane (1895) that reported no severe or life-threatening symptoms in healthy subjects at COHb concentrations of about 40%–56% were used as the basis for derivation of AEGL-3. The CFK model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb concentration of 40% at the end of exposure periods of 10- and 30 minutes and 1-, 4-, and 8 hours. The Committee discussed that the use of a ventilation rate of 13200 mL/min in the model adds some additional safety to the uncertainty factor used. A total uncertainty factor of 3 (intraspecies: 3) was based on the available reports on cases of myocardial infarction and stillbirth. Further comments noted that a statement was needed in the rationale that the derived exposure concentrations are protective for pregnant women (15% COHb as one of the therapy criteria) when exposed to CO. Additional comments included concern for the sensitive populations in other countries with Thalassemia; also the mechanism of cytochrome system poisoning. A motion was made by Steve Barbee and seconded by John Hinz to accept values of 1700 ppm, 600 ppm, 330 ppm, 150 ppm and 130 ppm, respectively, for the 10- and 30-minute and 1-, 4-, and 8-hour exposure values. The motion passed [YES:18; NO:3; ABSTAIN:1] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON MONOXIDE

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)
AEGL-3	1700 ppm (1900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)

NR = not recommended due to insufficient data

Sulfur Mustard (Agent-HD)
CAS Res. No. 505-60-2

Chemical Manager: Ken Still, U.S. Navy
Staff Scientist: Bob Young, ORNL Staff Scientist

Presentation of the chemical was given by Bob Young (Attachment 5) who discussed comments from the NAS/COT/AEGL for incorporation into the TSD. The COT agreed with the data but wanted to use an *n* of 3 for time scaling. Following the presentation that the NAC/AEGL Committee revise the AEGL-3 values for 10- and 30-minutes by calculating them using the *n*=3, the resulting values were 0.59 ppm and 0.41 ppm, respectively. George Rodgers moved acceptance of these values and was seconded by Mark McClanahan. The motion passed [YES: 21; NO: 1; ABSTAIN: 0] (Appendix E).

Phosphine, CAS Reg. No. 7803-51-2

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented an historical update of the phosphine AEGL (Attachment 6) from December 1996 (Draft 1) to the present January 2001 (Draft 6). There was extensive discussion of the *Federal Register* public comments (derivation of the exponent '*n*' for time scaling and use of a repeated-exposure study to derive an acute exposure value) and issues raised by a committee member (proper descriptions of human occupational exposure reports). Additionally, John Morawetz noted that "limited evidence suggested a death may have occurred at lower levels". Loren Koller moved to accept and Mark McClanahan seconded that AEGL-3 values be set as proposed.. The AEGL-3 levels were based on a NOEL for lethality in rats exposed to 18 ppm for 6 hours (Newton, 1991). Since animal lethality data suggested little species variability, an interspecies UF of 3 was applied; and, since human data suggested that children were more sensitive than adults, an intraspecies UF of 10 was applied (total UF=30). An empirically derived value of *n*=1, based on rat lethality data ranging from 1 to 6 hours, was utilized for time scaling. A vote was made on the 10- and 30- minute values and a second vote was made on the 1-, 4-, and 8-hour values. The 10- and 30-minute votes were: [YES: 16; NO: 5; ABSTAIN: 0], and the vote for 1-, 4-, and 8-hours was [YES; 22; NO: 0; ABSTAIN: 0]. All AEGL-3 values were accepted by NAC/AEGL (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHINE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4 ppm (5.6 mg/m^3)	4 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.5 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)
AEGL-3	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.9 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)

NR = not recommended due to insufficient data

Loren Koller moved and Mark McClanahan seconded that the Committee accept the AEGL-2 values as presented based on a decrease in body weight and a threshold for hematological effects in rats exposed to 10 ppm phosphine for 6 hours (Newton et al., 1991). Uncertainty factors and time scaling were as described above for AEGL-3. The vote was [YES: 14; NO: 6; ABSTAIN: 0] for the 10- and 30- minutes and 1-hour values. A second vote was taken on this motion for 4- and 8 hours [YES: 19; NO: 3; ABSTAIN: 0]. All values were accepted. (Appendix F).

The AEGL-1 was not established due to insufficient data.

Monochloroacetic acid, CAS Reg. No 79-11-8

Chemical Manager: Ernest Falke, U.S. EPA
Chemical Manager: Ruediger Bartsch, Horst Hollander and Reinhard Jung, German SFK Expert Group
Staff Scientist: Peter Griem, FoBiG Staff Scientist

Peter Griem presented an overview of the data on monochloroacetic acid (MCAA) to the Committee and covered the properties, production, uses, and toxicity concerns as well as relevant data from human and animal exposures (Attachment 7). Both the Maksimov and Dubinina (1974) study, reporting an irritation threshold of 1.48 ppm in humans, and the Clariant GmbH (2000) communication on occupational exposure were questioned for their inadequate data presentation and lack of effect. It was moved by Robert Benson and seconded by John Hinz to *not* establish AEGL-1 values for MCAA due to insufficient data [YES: 21; NO: 0; ABSTAIN:0] (Appendix G).

An insufficient database was also found for the AEGL-3. The only animal study reporting lethal effects after inhalation exposure (LC_{50} in rats of 46.8 ppm for 4 hours; Maksimov and Dubinina, 1974) was questioned for its inadequate data presentation. Several oral LD_{50} studies in animals were available; however, due to uncertainties regarding possible local effects of MCAA upon inhalation exposure, the group was reluctant to derive AEGL values by route-to-route extrapolation from an oral gavage study (BMD_{05} for lethality of 28.8 mg/kg/day; Hoechst AG,

1979). It was moved by Robert Benson and seconded by Judy Strickland that the AEGL-3 values *not* be established, again due to insufficient data [YES: 20; NO: 0; ABSTAIN: 1] (Appendix G).

For the AEGL-2, an inhalation study in rats (Dow Chemical Co., 1987) in which 12 rats exposed to an analytical concentration of 66 ppm for 1 hour showed eye squint and lethargy was discussed. Points of discussion were the large deviation of the analytical concentration from the nominal concentration of 964 ppm and the effect severity. The Committee considered the study appropriate to establish the AEGL-2 values. Time extrapolation was done by default assumptions (n=1 from 1 to 4 and 8 hours; n=3 for 30- and 10 minutes). A total uncertainty factor of 10 (interspecies: 3; intraspecies: 3) was used because the effect level was considered below that of an AEGL-2 and on basis of comparison with an older experimental study in humans using oral exposure. Judy Strickland moved and Steve Barbee seconded acceptance of the proposed values. The motion passed [YES: 22; NO: 0; ABSTAIN: 1] (Appendix G).

During the discussion a member of the Committee reported that he had done research on the central nervous system effects (damage of the blood-brain barrier) of MCAA and that severe effects had also been found after dermal exposure of rats and mice. This concern led to the proposal to include this information in the TSD and to have a statement in the summary tables concerning the extreme danger of dermal absorption of MCAA.

SUMMARY OF PROPOSED AEGL VALUES FOR MONOCHLOROACETIC ACID					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	12 ppm (47 mg/m^3)	8.3 ppm (33 mg/m^3)	6.6 ppm (26 mg/m^3)	1.7 ppm (6.7 mg/m^3)	0.83 ppm (3.3 mg/m^3)
AEGL-3	NR	NR	NR	NR	NR

NR = not recommended due to insufficient data

Xylenes, CAS Reg. No 1330-20-7

Chemical Manager: Loren Koller, Oregon State University
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

Claudia Troxel presented an overview of the mixed-, ortho-, para-, and meta- xylenes. (Attachment 8). The information presented suggested that blood-xylene concentrations are directly related to the central nervous system toxicity induced by xylene, and that xylene will equilibrate in the body for some period longer than 1 hour. Comments from George Rogers noted that not enough data from different species were available to allow an interspecies uncertainty factor of 1, and that narcosis appeared to be the endpoint of concern. John Morawetz also noted that these proposed values may not be protective except in a hospital setting.

A motion was made by Ernest Falke and seconded by Mark McClanahan to use 130 ppm for the AEGL-1 values from 10 minutes out to 8 hours; AEGL-2 values would be 430 ppm for the 1-, 4-, and 8-hour time points; AEGL-3 values would be 930 ppm for the 1-, 4-, and 8-hour time points. Based upon the data suggesting that blood-xylene concentrations will equilibrate in the body for some period longer than 1 hour, it was proposed to perform pharmacokinetic modeling to extrapolate xylene concentrations to the 10- and 30-minute exposure time points, and the proposal was amended to reconsider these 10- and 30-minute values for AEGL-2 and AEGL-3 at the next meeting. Dr. Ursula Gundert-Remy is to perform the modeling calculations. This motion passed [**AEGL-1:** YES: 16; NO: 4; ABSTAIN: 0; **AEGL-2:** YES: 16; NO: 4; ABSTAIN: 0; **AEGL-3:** YES:15; NO: 5; ABSTAIN: 0] (Appendix H).

SUMMARY OF PROPOSED AEGL VALUES FOR XYLENES					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)
AEGL-2	–* –	– –	430 ppm (1900 mg/m^3)	430 ppm (1900 mg/m^3)	430 ppm (1900 mg/m^3)
AEGL-3	– –	– –	930 ppm (4000 mg/m^3)	930 ppm (4000 mg/m^3)	930 ppm (4000 mg/m^3)

*Under development by NAC/AEGL committee

Propylene Oxide, CAS Reg. No.75-56-9

Chemical Manager: Jim Holler, ATSDR
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

Claudia Troxel presented data relating to using the original data previously evaluated with reference to epichlorhydrin or ethylene oxide (Attachment 9). A question of concern was that of the proper value of *n* to be used in the calculations. After noting the difference of the three above chemicals, it was moved by Jim Holler and seconded by Richard Thomas to continue with the previously presented AEGL 1-, 2-, and 3-level values based upon the *n* value of 1.2 for ethylene oxide. Having decided which *n* value to use, the issue of adding10-minute values was addressed. The AEGL-1 10-minute value was set equal to the 30-minute value because it was not considered appropriate to extrapolate from 8 hours to 10 minutes. The AEGL-2 and -3 values were extrapolated to the 10-minute exposure duration according to the SOP. This motion passed

[YES: 16; NO: 4; ABSTAIN: 0) (Appendix I). NAC/AEGL noted that additional public comments may be received on the value of *n* when propylene oxide is published in the *Federal Register*. The proposed values are:

SUMMARY OF PROPOSED AEGL VALUES FOR PROPYLENE OXIDE					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-hour**
AEGL-1	110 ppm (260 mg/m^3)	110 ppm (260 mg/m^3)	60 ppm (140 mg/m^3)	19 ppm (45 mg/m^3)	11 ppm (26 mg/m^3)
AEGL-2	1300 ppm (3100 mg/m^3)	510 ppm (1200 mg/m^3)	290 ppm (690 mg/m^3)	91 ppm (220 mg/m^3)	51 ppm (120 mg/m^3)
AEGL-3	2700 ppm (6400 mg/m^3)	1100 ppm (2600 mg/m^3)	610 ppm (1400 mg/m^3)	190 ppm (450 mg/m^3)	110 ppm (260 mg/m^3)

ISSUES REVISITED

HYDROGEN SULFIDE: CONFERENCE CALL

A presentation was made by Steve Barbee concerning the December 13, 2000, conference call on hydrogen sulfide (Attachment 10). A goal of the conference call was to finalize the selection of the data package to support AEGL-1 values in response to comments received from the COT AEGL subcommittee. These data sets will be reviewed by Cheryl Bast, Steve Barbee, and Zarena Post and will be discussed at a future AEGL committee meeting. The data set utilized by the WHO for derivation of the WHO hydrogen sulfide value was also discussed; the toxicity endpoint, eye irritation (from a 1939 occupational observation) was not supportable by a single statement of 20 ppm and 10 ppm with an uncertainty factor of 100 to obtain the 100 ppm value.

Tom Hornshaw drafted a letter to solicit any reports or studies documenting health effects meeting the definition of AEGL-1 and associated concentrations of H_2S (Attachment 11). This letter will be sent to members of the State and Territorial Air Pollution Program Administrators and the Association of Local Air Pollution Control Officials (STAPPA/ALAPCO) in January.

HYDROGEN CYANIDE: AEGL- 1

George Rodgers indicated the need to evaluate the data for only the AEGL-1 values (Attachment 12). Values were based on the Leeser et al. (1990) study; however, as pointed out by John Morawetz, the study is unclear at what exposure level the lack of health effects can be attributed to. The health effects are reported as aggregated for all workers in 8 job titles while the exposures are reported for each of 8 job titles (6 of the 8 job titles had geometric mean values at or below 0.5 ppm, one job title had a mean value of 1 ppm) (Attachment 13). The committee agreed the Leeser study generally supported values approved by NAC/AEGL. It is used as a supporting evidence for AEGL-1 values derived from El Ghawabi et al (1975). Two other

studies were also available for evaluation: El Ghawabi et al. (1975) and Grabois (1954). Committee comments included letting the approved values in July stand (values in ascending time order from 10 minutes to 8 hours of 2.5, 2.5, 2.0, 1.3, and 1.0 ppm, respectively), but adding more detailed comments on the sampling methods, in particular emphasizing personal monitoring (TWA samples) over short-term or area samples. It was suggested that additional details on sampling be added to the SOPs. George Rusch (Chair) had to meet a previously scheduled commitment and to facilitate completion of discussion of this chemical George appointed Ernie Falke to preside in his stead. Chairperson Ernie Falke asked for a show of hands to accept the values as passed in July and only clarify the rationale for the values. The show of hands was unanimous. No written ballot was made.

CONSIDERATION OF ODOR IN AEGL-1 DEVELOPMENT

Presentation of the subject on the use of odor in the development of an AEGL-1 was made by Marc Ruijten. Marc presented an organizational outline of the generic issue of whether odor is a valid endpoint for the AEGL-1 (Attachment 14). He outlined current needs to develop or refine the default approach for *n*, and discussed the current SOP. He sought help in various subcommittees in hopes of providing a position paper by end of January by a review in AEGL subcommittee in February or March, and discussion and resolution by NAC/AEGL in May. An update on progress will be in the proposed May meeting.

APPLICATION OF AEGL IN OCCUPATIONAL SETTINGS

The subject was presented by John Morawetz (Attachment 15). He pointed out the use of cases in which the exact exposures were in doubt and how perhaps the AEGL values may be in question due to the methods and ways various types of samples were collected and analyzed . It was commented that AEGLs are considered to be a once-in-a-lifetime exposure event for the general public and do not take the place of STELs in the workforce. John was hopeful that resolution will be available to the AEGL Committee in May. He gave the example of a Bromine release and the use of AEGL-2 values in recommendations to allow the return of workers to areas of work. He also reviewed the major organizations that set occupational limits (OSHA, NIOSH, ACGH) and their applicability in all occupational settings, including emergency response.

VISITORS

Dr. George Woodall presented comments from the American Petroleum Institute on the AEGL values for H_2S. He offered the possibility of using other studies to set the values. Attached is the material Dr. Woodall handed out to accompany his talk (Attachment 16).

Dr. Bill Kojola, Industrial Hygienist, Dept. of Occupational Safety and Health, AFL-CIO,

presented comments represented comments stressing that AEGL values for community exposures should not be used in occupational settings.

Dr. Gerald Kennedy (DuPont) also presented comments on the potential problems in applying AEGL values to occupational settings.

ADMINISTRATIVE ISSUES

The next meeting was considered for May at this same meeting place with the dates and confirmation to be provided at a later time.

Meeting highlights were prepared by Hank Spencer and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC/AEGL Meeting No. 20 Agenda
2. NAC/AEGL Meeting No. 20 Attendee List
3. Phenol: Consideration of data for AEGL values
4. Carbon Monoxide: Consideration of data for AEGL values
5. Sulfur Mustard: Comment incorporation from NAS/AEGL
6. Phosphine: Review of data for AEGL values
7. Xylenes: Review of data
8. Monochloroacetic Acid: Consideration of data for AEGL values
9. Propylene Oxide: Reconsideration of the *n* values
10. Hydrogen Sulfide: Revisit, conference call highlight
11. Solicitation of H2S reports by Thomas Hornshaw
12. Hydrogen Cyanide: Consideration of the data for AEGL-1
13. Hydrogen Cyanide Exposure by Job Title Lesser, 1990
14. Consideration of odor in AEGL-1 development
15. Application of AEGLs in occupational settings
16. Comments of the American Petroleum Institute on AEGL values for Hydrogen Sulfide

LIST OF APPENDICES

A. Ballot for Approval of NAC/AEGL Meeting 19 Highlights
B. Revised NAC/AEGL Meeting18 Highlights
C. Ballot for Phenol
D. Ballot for Carbon Monoxide
E. Ballot for Sulfur Mustard
F. Ballot for Phosphine
G. Ballot for Monochloroacetic Acid
H. Ballot for Xylenes
I. Ballot for Propylene Oxide

UNANIMOUS

NAC/AEGL-20

NAC/AEGL Meeting 21: June 11-13, 2001

Appendix B

Chemical: **CAS Reg. No.:**

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	✓		
Steven Barbee	✓		
Lynn Beasley	✓		
David Belluck			
Robert Benson			
Jonathan Borak	✓		
William Bress	✓		
George Cushmac	✓		
Ernest Falke	✓		
Larry Gephart	✓		
John Hinz	✓		
Jim Holler	✓		
Thomas C. Hornshaw	✓		
Nancy Kim	✓		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Loren Koller	✓		
Glenn Leach	✓		
Mark McClanahan	✓		
John S. Morawetz	✓		
Richard W. Neimeier	✓		
Marinelle Payton	✓		
Zarena Post	✓		
George Rodgers	✓		
George Rusch, Chair	✓		
Robert Snyder			
Thomas Sobotka			
Kenneth Still	✓		
Richard Thomas	✓		
Thomas Tuccinardi/ Doan Hansen	✓		
TALLY			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: McClanahan **Second:** Hansen

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/11/01

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: CHLORINE DIOXIDE ClO_2 **CAS Reg. No.:** 10049-04-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N	Y	Loren Koller	Y	Y	N
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	Y	Y	Y	Mark McClanahan	Y	Y	N
David Belluck	A	A	A	John S. Morawetz	Y	N	Y
Robert Benson	Y	N	Y	Richard W. Neimeier	Y	Y	Y
Jonathan Borak	P	P	Y	Marinelle Payton	Y	P	Y
William Bress	Y	Y	Y	Zarena Post	Y	Y	Y
George Cushmac	Y	Y	Y	George Rodgers	Y	Y	Y
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	Y	Y	Y	Robert Snyder	Y	Y	Y
John Hinz	Y	P	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	Y	Y	Y
Thomas C. Hornshaw	P	N	Y	Richard Thomas	Y	N	Y
Nancy Kim	Y	Y	Y				
				~~Thomas Tuccinardi~~/ Doan Hansen	Y	N	Y
				TALLY	24/24	17/23	24/26

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	* NR , ( )	NR , ( )	NR , ( )	NR , ( )	NR , ( )
AEGL 2	~~0.90~~ 0.97 , ( )	0.67 , ( )	0.53 , ( )	0.32 , ( )	0.21 , ( )
AEGL 3	2.9 , ( )	2.0 , ( )	1.6 , ( )	0.97 , ( )	0.63 , ( )

* NR recommended due to lack of data.

AEGL 1 Motion: Falke **Second:** Benson

AEGL 2 Motion: McClanahan **Second:** Gephart

AEGL 3 Motion: Snyder **Second:** Hinz

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/12/01

NAC/AEGL Meeting 21: June 11-13, 2001

Appendix D

Me_2NCH (O above C)

Chemical: N, N-DIMETHYLFORMAMIDE **CAS Reg. No.:** 68-12-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N	N	Loren Koller	Y	Y	Y
Steven Barbee	N	Y	Y	Glenn Leach	Y	Y	N
Lynn Beasley	Y	Y	Y	Mark McClanahan	N	N	N
David Belluck	A	A	A	John S. Morawetz	Y	N	P
Robert Benson	Y	P	N	Richard W. Neimeier	Y	N	N
Jonathan Borak	Y	Y	P	Marinelle Payton	N	P	Y
William Bress	Y	Y	Y	Zarena Post	Y	Y	P
George Cushmac	Y	Y	Y	George Rodgers	Y	Y	N
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	N	Y	Y	Robert Snyder	Y	P	Y
John Hinz	Y	N	P	Thomas Sobotka	A	A	A
Jim Holler	Y	N	Y	Kenneth Still	Y	Y	Y
Thomas C. Hornshaw	Y	P	P	Richard Thomas	A	N	Y
Nancy Kim	Y	P	Y				
				~~Thomas Tuccinardi~~/ Doan Hansen	N	Y	Y
				TALLY	20/25	14/21	15/21

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	*NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	160 ,( )	110 ,( )	90 ,( )	55 ,( )	38 ,( )
AEGL 3	320 ,( )	220 ,( )	180 ,( )	110 ,( )	76 ,( )

* NR = Not recommended due to lack of data.

AEGL 1 Motion: Falke **Second:** Rodgers

AEGL 2 Motion: J. Borak **Second:** L. Koller

AEGL 3 Motion: L. Koller **Second:** R. Thomas

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/12/01

Chemical: PHOSGENE **CAS Reg. No.:** 75-44-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		Y		Loren Koller		Y	
Steven Barbee		Y		Glenn Leach		Y	
Lynn Beasley		Y		Mark McClanahan		Y	
David Belluck		A		John S. Morawetz		Y	
Robert Benson		P		Richard W. Neimeier		Y	
Jonathan Borak		Y		Marinelle Payton		Y	
William Bress		Y		Zarena Post		Y	
George Cushmac		Y		George Rodgers		Y	
Ernest Falke		Y		George Rusch, Chair		Y	
Larry Gephart		Y		Robert Snyder		A	
John Hinz		Y		Thomas Sobotka		A	
Jim Holler		Y		Kenneth Still		Y	
Thomas C. Hornshaw		Y		Richard Thomas		A	
Nancy Kim		Y					
				~~Thomas Tuccinardi~~/ Doan Hansen		Y	
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, (2.5)	NR, (1.2)	NR, ( )	NR, ( )
AEGL 2	0.60, (2.5)	0.60, (~~2.5~~)	0.30, (~~1.3~~)	0.08, (~~0.33~~ 0.5)	0.04, (0.16)
AEGL 3	3.6, (15)	1.5, (6.2)	0.75, (3.1)	0.20, (0.82)	0.09, (0.34)

AEGL 1 Motion: _____ **Second:** _____

* **AEGL 2 Motion:** RODGERS **Second:** FALKE

** **AEGL 3 Motion:** HINZ **Second:** McCLANAHAN

* MAINTAIN 0.60 ppm FOR 10 MIN AEGL-2 IN INTERIM

** RAISE ALL PHOSGENE AEGL VALUES TO

Approved by Chair: _____ **DFO:** _____ **Date:** 6/11/01

Appendix F

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: HYDROGEN SULFIDE H_2S **CAS Reg. No.:** 7783-06-4

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	A		
Robert Benson	Y		
Jonathan Borak	A		
William Bress	Y		
George Cushmac	Y		
Ernest Falke	Y		
Larry Gephart	Y		
John Hinz	Y		
Jim Holler	Y		
Thomas C. Hornshaw	Y		
Nancy Kim	P		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Loren Koller	Y		
Glenn Leach	Y		
Mark McClanahan	Y		
John S. Morawetz	N		
Richard W. Neimeier	P		
Marinelle Payton	N		
Zarena Post	N		
George Rodgers	Y		
George Rusch, Chair	X		
Robert Snyder	P		
Thomas Sobotka	A		
Kenneth Still	Y		
Richard Thomas	Y		
~~Thomas Tuccinardi~~ Doan Hansen	Y		
TALLY	18/22		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	.25 ,( )	.20 ,( )	.17 ,( )	.12 ,( )	.11 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: Hinz **Second:** Rodgers

AEGL 2 Motion: _____ **Second:** _____

Second: _____

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL # of pages ▶ 1

To	From
Po Tung Lu	Paul Tobin
Dept./Agency	Phone #
OPPT/LIFE SCI	202 260-1736
Fax #	Fax #
865 241-0397	0981

NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

FO: Paul Tobin **Date:** 6/12/01

Proposed → Interim Ballot

Appendix G

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: DIBORANE **CAS Reg. No.:** 19287-45-7

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	A		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	A		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Holler **Second:** Hansen / McClanahan

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/11/01

Proposed → Interim Ballot

Appendix H

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: BORON TRICHLORIDE BCl_3 **CAS Reg. No.:** 10294-34-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	P			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	A		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	A		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: MCCLANAHAN **Second:** HINZ

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/14/01

Proposed → Interim Ballot

Appendix I

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: CARBON MONOXIDE CO **CAS Reg. No.:**

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	A		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	N		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	A		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: HINZ **Second:** McCLANAHAN

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/11/01

Proposed to Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Appendix J

Chemical: CHLOROMETHYL METHYL ETHER **CAS Reg. No.:** 107-30-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	A		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	A		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas~~ Tuccinardi/ Doan Hansen	Y		
				TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: HINZ **Second:** McCLANAHAN

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/11/01

Proposed - Interim Ballot

Appendix K

NAC/AEGL Meeting 21: June 11-13, 2001

CIS-C $(Cl)_3$

Chemical: PERCHLOROMETHYL MERCAPTAN **CAS Reg. No.:** 594-42-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	A		
Jonathan Borak	A			Marinelle Payton	A		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	A		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY	15/16		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: Hinz **Second:** McClanahan

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/01

Appendix L

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: TETRANITROMETHANE $(O_2N)_4C$ **CAS Reg. No.:** 509-14-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	A		
Jonathan Borak	A			Marinelle Payton	A		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	A		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY	18/18		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: McClanahan **Second:** Bress

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/01

Proposed → Interim Values

Appendix M

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: TOLUENE ϕCH_3 **CAS Reg. No.:** 108-88-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	A		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	Y		
Nancy Kim	Y						
				~~Thomas Tuccinardi/~~ Doan Hansen	Y		
				TALLY	23/23		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: J. Gephart **Second:** R. Thomas

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/12/01

Proposed Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Appendix N

Chemical: FURAN (2) **CAS Reg. No.:**

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	A		
William Bress	Y			Zarena Post	Y		
George Cushmac	A			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi/~~ Doan Hansen	Y		
				TALLY	19/19		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: B. Rodgers **Second:** _____

AEGL 2 Motion: McClanahan **Second:** Barbee

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/12/01

Proposed Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Appendix O

$Cl_2C=CCl_2$

Chemical: TETRACHLOROETHYLENE **CAS Reg. No.:** 127-18-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	A		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi/~~ Doan Hansen	Y		
				TALLY	22/22		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	50 ,( )	50 ,( )	35 ,( )	18 ,( )	12 ,( )
AEGL 2	230 ,( )	230 ,( )	230 ,( )	120 ,( )	81 ,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: ** Rodgers **Second:** McClanahan

AEGL 2 Motion: * Benson **Second:** Morawetz

AEGL 3 Motion: ~~Benson~~ **Second:** ~~Morawetz~~

* Change in AEGL 10 + 30 min

** Raise to Interim

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/12/01

PROPOSED → INTERIM

Appendix P

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: ALLYL ALCOHOL (=OH) **CAS Reg. No.:** 107-18-6

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	A		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	Y		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	Y			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	Y		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	Y		
				TALLY	22/23		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Morawetz **Second:** McClanahan

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/12/01

Proposed → Interim Ballot

Appendix Q

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: GA-TABUN [redacted] $EtO-\overset{O}{\overset{\|}{P}}(CN)-NMe_2$ **CAS Reg. No.:** 77-81-6

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	N		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	N		
				TALLY	17/22		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

ALL 6 AGENTS → INTERIM, BUT BRING BACK IF REVIEW OF LIT. INFO MERITS & VX

AEGL 1 Motion: Bress **Second:** Leach

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/13/01

Proposed Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: GB SARIN $CH_3P(=O)(F)-O-CHMe_2$ **CAS Reg. No.:** 107-44-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	N		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	N		
				TALLY	19/22		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )

All G Agents → INTERIM

AEGL 1 Motion: Bress **Second:** Leach

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 9/13/01

Proposed Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: GD-SOMAN $CH_3P(=O)(F)OCH(CH_3)-tBu$ **CAS Reg. No.:** 96-64-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	N		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				Thomas Tuccinardi/ Doan Hansen	N		
				TALLY	19/22		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Bress **Second:** Leach

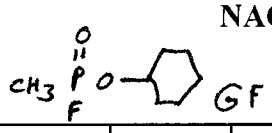
AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/01

Proposed to Interim Bulk

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical:  GF **CAS Reg. No.:** 329-99-7

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	N		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~ Doan Hansen	N		
				TALLY	19/22		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Bress **Second:** Leach

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/01

Proposed Interim Ballot

NAC/AEGL Meeting 21: June 11-13, 2001

Chemical: VX $CH_3O-\overset{O}{\overset{\|}{P}}(CH_3CH_2O)-S\,CH_2CH_2\,N(CHMe_2)_2$ **CAS Reg. No.:** 50782-69-9

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Loren Koller	Y		
Steven Barbee	Y			Glenn Leach	Y		
Lynn Beasley	Y			Mark McClanahan	Y		
David Belluck	A			John S. Morawetz	A		
Robert Benson	Y			Richard W. Neimeier	Y		
Jonathan Borak	A			Marinelle Payton	Y		
William Bress	Y			Zarena Post	Y		
George Cushmac	Y			George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	N		
John Hinz	Y			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	Y		
Thomas C. Hornshaw	Y			Richard Thomas	A		
Nancy Kim	Y						
				~~Thomas Tuccinardi~~/ Doan Hansen	N		
				TALLY	19/22		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )

AEGL 1 Motion: Bress **Second:** Leach

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/01